Original Article

Effect of Omega-3 Fatty Acid Use on Sepsis and Mortality in Patients with Covıd-19

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Abstract

Background: This study aimed to investigate the effects of omega-3 fatty acid use on sepsis and mortality in patients treated for COVİD-19 disease in the intensive care unit (ICU) based on clinical and laboratory results. **Aim:** To determine the effect of omega-3 fatty acid use on sepsis and mortality in patients with COVİD-19. **Patients and Methods:** A total of 80 patients with confirmed COVİD-19 infection who were hospitalized in the ICU of Ankara City Hospital, received (n = 40) or did not receive (n = 40) omega-3 fatty acid dietary supplementation, were included in this single-center, retrospective study. The clinical and laboratory data of eligible patients were extracted from the hospital records. **Results:** The mean age was 65.5 (13.6). The mean length of stay in the intensive care unit was 11.5 (6.3) days. Mortality and sepsis development rates were similar in the groups. The frequency of patients who received pulse steroid therapy was higher in the group of patients who did not receive omega-3 ($P < 0.05$). Hypertension was more common in the patient group receiving omega-3 supplements ($P < 0.05$). Mean procalcitonin and interleukin-6 (IL-6) levels were significantly lower in patients who received omega-3 supplements compared to those who did not receive supplements ($P < 0.001$ and $P < 0.05$). Mean prothrombin time (PT) was shorter in patients receiving omega-3 supplementation ($P < 0.05$). **Conclusions:** Study results obtained in this study indicate that providing omega-3 fatty acid supplements may be beneficial to patients with severe COVİD-19, however further research with large-scale randomized controlled trials is necessary.

Keywords: *COVİD-19, fatty acid, ıntensive care, omega-3, SARS-CoV-2*

Introduction

At the end of 2019, COVID-19, which is the illness caused by the novel SARS-CoV-2 virus, was first identified in Wuhan city, China, and then spread worldwide. World Health Organization (WHO) declared the pandemic of COVID-19 in March 2020. This disease still represents an important threat to healthcare globally.[1] The majority of the symptomatic individuals with COVID-19 have relatively mild disease, however, 14% usually develop severe disease with significant symptoms such as dyspnea, hypoxia, and lung involvement. Five percent of the patients develop critical disease which is characterized by respiratory failure and/or multiorgan dysfunction.[2] During the severe COVID-19 disease, inflammatory cytokines such as TNF-alpha, interleukin-1β, and interleukin-6 are rapidly released and cause a "cytokine storm".[3] Older age (>65 years), chronic lung disease, cardiovascular diseases, and diabetes mellitus are among the associated risk factors related to severe and critical COVID-19 disease.[4]

The nutritional status of the patient plays an important role in fighting the virus during viral infections.[5] It is known that malnourished individuals are more prone to

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infections since nutritional deficiencies harm the immune system.[6] Proper nutrition is suggested for patients with COVID-19 since it reduces inflammation and oxidative stress and improves the immune system.[7]

Omega-3 fatty acids, which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are polyunsaturated fatty acids, and they have favorable effects on the immune system and inflammation.[8] Controversial suggestions are available in the literature regarding the usage of omega-3 fatty acids in COVID-19 patients. European Society for Parenteral and Enteral Nutrition provided an expert opinion and mentioned that enteral usage of omega-3 fatty acids may improve oxygenation in patients with COVID-19, however strong evidence is missing.[9] On the other hand, study reports that are discussed in a systematic review mention that EPA and DHA can increase the susceptibility of cellular membranes to non-enzymatic oxidation, and this may lead to toxic oxidation and increase oxidative stress.[10]

Considering the beneficial effects of omega-3 fatty acids on the immune system and controversial suggestions, we aimed to investigate the effect of omega-3 fatty acid use on clinical outcomes such as sepsis and mortality in patients treated for COVID-19 disease in the intensive care unit (ICU).

Materials and Methods

This single-center, retrospective study was conducted in the ICU of Ankara City Hospital, Turkey. The study was carried out under the Helsinki Declaration and local laws and regulations. Since this was a retrospective study, obtaining written informed consent from the patients was not required. Before the initiation of the study, ethics committee approval (No: E2-21-1049) was obtained from the ethics committee of Ankara City Hospital on December 8, 2021.

A total of 80 patients with confirmed COVID-19 infection who were hospitalized in the ICU of the study center between December 2021 and January 2022, received (n = 40) or did not receive (n = 40) omega-3 fatty acid dietary supplementation, were included in this study. Inclusion criteria were age ≥18 years, cytokine storm score (CSs) ≥2, and serum procalcitonin (PCT) level ≤0.5 ng/mL. Patients who did not receive antibiotic treatment or who developed sepsis were excluded.

Patients were mainly categorized into two groups according to the administration of additional omega-3 fatty acid dietary supplementation. Omega 3 fatty acid supplementation containing EPA and DHA in 100 ml infusion emulsion was administered to patients who required additional dietary supplementation. Clinical and laboratory data were recorded retrospectively from the hospital records that included categorical variables (such as gender [male/female], intubation [yes/no], mechanic ventilation [yes/no], etc.) and continuous variables (such as age [years], length of stay in the ICU [days], etc.).

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, USA). Continuous variables were presented with mean, standard deviation, and minimum-maximum values, whereas categorical variables were presented with frequency (n) and percentages (%). The chi-The square test was used for comparing variables with two categories and the t-test was used for the comparison of continuous variables. Test results with a P value < 0.05 were considered statistically significant.

Results

A total of 80 patients with a confirmed diagnosis of COVID-19 infection who were hospitalized in the ICU of our hospital were included in this retrospective analysis. Of these, 40 patients received additional

Table 1: Overall patient characteristics

	Male	Female
Gender, *n* (%)	56 (70)	24 (30)
	Mean (±SD)	**Range**
Age (years)	65.5 (±13.6)	19-88
ICU stay (days)	11.5 (±6.3)	3-41
Time to intubation (days)	3.5 (±5.4)	0-30
APACHE score	8.4 (±4.7)	2-26
SOFA score	4.2 (±2.5)	2-15
Ferritin (ng/mL)	765.5 (±525)	23-2584
CRP (ng/mL)	123.6 (±73.6)	8-419
Procalcitonin (ng/mL)	0.6 (±1.7)	0-9.3
IL-6 (pg/mL)	61.2 (±124.9)	2-1000
D-Dimer (ng/mL)	3.4 (±6.6)	0.3-35.2
aPTT (seconds)	23.7 (±3.6)	18-39
PT (seconds)	12.5 (±1.7)	10-19
LDH (U/L)	529.4 (±247.4)	196-2058
Cytokine Storm Score	3.2 (±1)	1-5
Urea (mg/dL)	70.7 (±43.8)	20-227
Creatinine (mg/dL)	1.3 (±1.1)	0.5-7.3
GFR (mL/min/1.73 m^2)	71.9 (±29.4)	5.1-133
ALT (U/L)	54.9 (±53.5)	8-417
AST (U/L)	76.4 (±142)	13-1286
Lymphocyte (10^9/L)	0.6 (±0.4)	0.2-2.6
WBC (10^9/L)	9.6 (±3.6)	3.1-24
NEU (10^9/L)	8.4 (±3.5)	2.4-23.3
HB (g/dL)	13.4 (±1.6)	8-16.6
PLT (10^9/L)	293.5 (±109.5)	21-572

ICU: Intensive care unit, SD: Standard deviation

Table 2: Comparison of omega-3 dietary supplementation for categorical variables

	No Omega-3 Fatty Acid Supplementation (*n*)	Omega-3 Fatty Acid Supplementation (*n*)	Total (*n*)	*P**
Intravenous Immunoglobulin				
Yes	1	2	3	0.556
No	39	38	77	
Anakinra				
Yes	2	5	7	0.235
No	38	35	73	
Steroid				
Pulse	40	34	74	0.011
Low dose	0	6	6	
Sepsis Development				
Yes	21	20	41	0.599
No	19	20	39	
Intubation				
Yes	19	22	41	0.502
No	21	18	39	
Gender				
Male	30	26	56	0.329
Female	10	14	24	
Secondary Infection				
Yes	24	17	41	0.117
No	16	23	39	
Mortality				
Exitus	16	22	38	0.179
Discharged	24	18	42	
High Flow Nasal Oxygen				
Yes	33	35	68	0.531
No	7	5	12	
Invasive Mechanic Ventilation				
Yes	19	20	39	0.823
No	21	20	41	
Non-invasive Mechanic Ventilation				
Yes	2	0	2	0.152
No	38	40	78	
Diabetes Mellitus				
Yes	9	9	18	1.000
No	31	31	62	
Hypertension				
Yes	15	24	39	0.044
No	25	16	41	
Chronic Pulmonary Disease				
Yes	6	7	13	0.762
No	34	33	67	
Chronic Obstructive Pulmonary Disease				
Yes	4	6	10	0.499
No	36	34	70	
Renal Disease				
Yes	3	6	9	0.288
No	37	34	71	
Cancer				
Yes	1	1	2	1.000
No	39	39	78	
Neurologic Disorder				
Yes	2	4	6	0.396
No	38	36	74	

*Chi-square test

Table 3: Comparison of omega-3 dietary supplementation for continuous variables

	No Omega-3 Fatty Acid supplementation (mean)	Omega-3 Fatty Acid supplementation (mean)	*P**
Age (years)	62.0	69.0	0.309
Length of stay (days)	12.0	11.0	0.618
Length of intubation (days)	3.6	3.5	0.897
APACHE score	8.2	8.7	0.174
SOFA score	4.2	4.3	0.397
Ferritin	801.3	729.7	0.389
CRP	147.7	99.4	0.412
Procalcitonin (ng/mL)	1.0	0.2	<0.001
IL-6 (pg/mL)	91.5	30.9	0.024
D-Dimer	3.8	3.0	0.199
aPTT	24.0	23.4	0.845
PT	12.7	12.3	0.006
LDH	560.0	498.9	0.300
Cytokine Storm Score	3.4	3.1	0.082
Urea	64.1	77.4	0.570
Creatinine	1.2	1.3	0.634
GFR	78.1	65.8	0.591
ALT	68.8	41.0	0.166
AST	98.4	54.4	0.122
Lymphocyte	0.6	0.6	0.183
WBC	9.7	9.5	0.115
NEU	8.5	8.3	0.091
HB	13.4	13.3	0.371
PLT	298.9	288.1	0.109

**t*-test

Table 4: Comparison of omega-3 dietary supplementation for time to development of sepsis

	Time to Development of Sepsis (days)												Total
	0	1	2	3	4	5	6	7	8	9	10	11	
Omega-3 Fatty Acid Supplementation (*n*)													
No	19	3	4	2	2	1	2	2	0	0	3	2	40
Yes	20	0	4	4	3	2	0	2	2	1	0	2	40
Total	39	3	8	6	5	3	2	4	2	1	3	4	80

omega-3 fatty acids dietary supplementation in addition to their standard of care whereas 40 patients received only standard treatment for COVID-19. Most of the patients hospitalized in the ICU due to COVID-19 were male (70%). The mean patient age was 65.5 (±13.6) years ranging between 19 and 88 years. The duration of ICU stay ranged between 3 to 41 days and the mean duration of ICU stay was 11.5 (±6.3) days. Other clinical and laboratory parameters recorded at the time of hospitalization are presented in Table 1.

After categorizing the patients (receiving or not receiving additional omega-3 fatty acid dietary supplementation) our study results indicated statistically significant differences between patient groups. The frequency of patients who received pulse steroid treatment was higher in the patient group who did not receive omega-3 supplementation (Table 2, $P = 0.011$). Additionally, hypertension was present more frequently in the patient group receiving omega-3 supplementation (Table 2, $P = 0.044$). Laboratory results [Table 3] revealed that mean procalcitonin and interleukin-6 (IL-6) levels were significantly lower in patients receiving omega-3 compared to the patient group who did not receive additional omega-3 dietary supplementation (0.2 vs. 1.0 ng/mL, $P < 0.001$ for procalcitonin and 30.9 vs. 91.5 pg/mL, $P = 0.024$ for IL-6). Similarly, mean prothrombin time (PT) was shorter in patients receiving omega-3 supplementation (12.3 vs. 12.7 seconds, $P = 0.006$).

Other evaluated clinical and laboratory parameters, including mortality and time to development of sepsis [Table 4], were similar in patient groups receiving or not receiving additional omega-3 fatty acid dietary supplementation ($P > 0.05$).

Discussion

Our study results did not indicate a significant effect of omega-3 fatty acid use on sepsis and mortality in patients treated for COVID-19 in the intensive care unit (ICU). However, we detected significant differences between patients receiving or not receiving enriched nutrition with omega-3 fatty acids for some of the investigated clinical and laboratory parameters.

Doaei *et al*. [2021[11]] conducted a double-blind, randomized clinical trial with 128 critically ill patients with COVID-19 and investigated the effect of omega-3 fatty acid supplementation on the clinical and laboratory parameters of these patients. In their study 86 patients in the intervention group received 1000 mg omega-3 daily containing 400 mg EPAs and 200 mg DHAs for 14 days whereas the control group (n = 42) received standard of care. Their study results show that the omega-3 group had a significantly higher survival rate. Approximately 21% of the patients in the omega-3 group (n = 6), and 3% of the patients in the control group (n = 2) survived at least 1 month in their study (P = 0.003). Previously similar results were reported regarding the effect of omega-3 supplementation in various patient populations. In a prospective cohort study, Mozaffarian *et al*.[12] investigated the associations of plasma omega-3 levels with mortality in healthy older adults and reported that higher omega-3 levels are associated with lower mortality. Nagata *et al*.[13] examined the effect of various food supplements on mortality in a cohort of approximately 30000 individuals and their results indicated that products containing omega-3 fatty acids were significantly related to lower mortality in women, but not in men. In their observational cohort study, Eide *et al*.[14] investigated associations between omega-3 fatty acid levels and mortality in 1990 Norwegian renal transplant recipients and reported that higher plasma omega-3 levels were associated with a higher survival rate. Despite the higher discharge rate observed in the patient group that received omega-3 supplementation, we did not detect a lower mortality rate in the same group compared to the patients who did not receive additional omega-3 supplementation. Possible reasons for this outcome may be our small sample size and our retrospective design.

A total of 12 studies were included in a systemic review with a meta-analysis in which the benefits of omega-3 fatty acid supplementation to outcomes of patients with sepsis (n = 721) were evaluated, Results of this meta-analysis demonstrated that supplementation of omega-3 fatty acids was beneficial to patients with sepsis.[15] Furthermore, intravenous administration of omega-3 fatty acid supplementation was evaluated in a recent study in patients with acute-on-chronic liver failure, and results revealed that omega-3 fatty acids were safe and effective in reducing inflammation and sepsis.[16] Results of another recent meta-analysis, which included 49 randomized controlled clinical trials, showed that omega-3 fatty acid supplementation reduces the risk of infection and sepsis by 40% and 50%, respectively.[17] On the contrary, our study results did not indicate an effect of omega-3 fatty acid supplementation on reducing sepsis in patients with COVID-19. Similar to the results of mortality, we think that reason for this outcome may be related to our small sample size and omega-3 dose levels.

In a double-blind, randomized, controlled clinical trial conducted in Scotland, 64 patients with mild rheumatoid arthritis received either the study drug (capsules containing EPA and DHA) or a placebo for 12 months. Patients were asked to reduce their non-steroidal anti-inflammatory drug (NSAID) dosage gradually if there was no worsening of their symptoms. A significant reduction in NSAID usage was observed in patients receiving EPA/DHA treatment when compared with the placebo group starting from month 3 and this effect was at a maximum level at month 12. Results of this study conducted in Scotland indicated that patients with mild rheumatoid arthritis may reduce their steroid usage without experiencing any worsening in their symptoms and laboratory parameters while they are receiving omega-3 fatty acids.[18] Rosenbaum *et al*.[19] conducted a literature review to investigate whether dietary supplements can be used effectively to manage disease activity in patients with osteoarthritis and rheumatoid arthritis. After reviewing 16 efficacy studies they reported that the efficacy of these supplements is still unclear and requires more well-designed research. A report suggests the superiority of steroid treatment against omega-3 fatty acid enrichment in patients with advanced cancer in the treatment of anorexia and cachexia.[20] To our knowledge, there's no report evaluating the efficacy of omega-3 fatty acid supplementation in hospitalized patients with COVID-19 based on steroid usage. Even though our study results suggest that omega-3 fatty acid supplementation may reduce steroid usage in these patients, this outcome should be interpreted with caution.

In our study, the mean procalcitonin and interleukin-6 (IL-6) levels were significantly lower in patients receiving omega-3 compared to the patient group who did not receive additional omega-3 dietary supplementation (0.2 vs. 1.0 ng/mL, $P < 0.001$ for procalcitonin and 30.9 vs. 91.5 pg/mL, $P = 0.024$ for IL-6). These results are in line with the results provided by Shakoor *et al*.[8] and Kulkarni *et al*.[16]

In the present study, the mean PT was shorter in patients receiving omega-3 supplementation. Although this result seems to be contrary to the positive effect of omega-3 supplementation, it is a situation that can be seen in patients with COVID-19.[21]

A recent cross-sectional case-control study investigated effects of omega-3 fatty acids by determining the omega-3 index (O3I) in the blood of patients with severe COVID-19 Zapata *et al*.[22] The O3I is defined as the omega-3 fatty acid (EPA and DHA) content of the erythrocyte cell membrane and in healthy individuals, the rate of O3I should be >8%. The results of this study showed that patients with COVID-19 had low O3I levels compared to the healthy controls. Furthermore, an inverse association was found between O3I and mechanical ventilation and mortality. To our knowledge, there are not many clinical studies evaluating the effects of omega-3 fatty acids on mechanical ventilation in patients with COVID-19. In the present study patients receiving omega-3 fatty acid supplements did not receive mechanical ventilation, however, our data did not permit obtaining a significant difference between the two patient groups.

Our study has some limitations. First, our retrospective design did not allow us to standardize all procedures related to the parameters evaluated in this study. Even though this was a single-center study, and the procedures followed in our hospital are clear, randomized controlled trials can provide more reliable results. Second, our sample size can be considered low which may have led to not obtaining significant statistical results.

Conclusion

Even though we did not detect any significant difference between patients receiving or not receiving omega-3 fatty acid supplements in terms of mortality and sepsis, our results suggest some benefits of omega-3 supplements in terms of some laboratory parameters. In conclusion, our study results indicate that providing omega-3 fatty acid supplements may be beneficial to patients with severe COVID-19, however, further research with large-scale randomized controlled trials is necessary.

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Ethics statement

This study has been approved by the Local Ethics Committee of Ankara City Hospital and is following the ethical standards of the Declaration of Helsinki.

Patient consent statement

Written informed consent was obtained from all participants.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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