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Original Article

The Role of Omega-3 on The IL-6 Levels, Malondialdehyde, and Clinical Improvement in Adults with Community-Acquired Pneumonia

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Abstract

Background: Acute lung parenchyema infection known as pneumonia can be carried on by a variety of microorganisms, including bacteria, viruses, fungi, and parasites. Globally, community-acquired pneumonia is a major factor in morbidity, mortality, and health issues. Malondialdehyde (MDA) is a marker of oxidative stress in pneumonia patients, and interleukin 6 (IL-6) is a marker of the inflammatory process. Effect of omega-3 as an immunomodulator, anti-inflammatory, and antioxidant that may be implemented as an adjunctive therapy in patients with community-acquired pneumonia.

Methods: Clinical trial research with true experimental method and using pretest posttest design. The study sample consisted of 30 community acquired pneumonia patients who were hospitalized at Moewardi hospital in Surakarta and dr. Soehadi Prijonegoro hospital in Sragen from August – September 2022 by consecutive sampling. The control group (n=15) received standard therapy and the treatment group (n=15) received standard therapy plus omega-3 at a dose 1600mg/day. IL-6 and MDA levels were measured when the subject was admission to the hospital and there was clinical improvement.

Results: There was a significant difference between the treatment group compared to the control group in reducing IL-6 levels ($p = 0.001$), decreasing MDA levels ($p = 0.001$) and the duration of clinical improvement ($p = 0.042$). There was a moderate correlation in the decrease in IL-6 ($R = 0.480$) and MDA ($R = 0.459$) while the duration of clinical improvement had a strong correlation ($R = 0.756$) in the treatment group.

Conclusion: Supplementation of Omega-3 was proven in community acquired pneumonia patients can reduce IL-6, MDA levels and duration of clinical improvement.

Keywords: Omega-3, Community-acquired pneumonia, IL-6, MDA, Clinical improvement

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INTRODUCTION

Pneumonia is defined as an acute lung parenchymal infection carried on by a variety of pathogens, including bacteria, viruses, fungi, and parasites. Community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP) are the types of pneumonia (VAP).[1,2,3] Community-acquired pneumonia (CAP) is an acute inflammation of the lung parenchyma that is obtained in the community.[1,2] Despite advancements in its management during the past ten years, CAP remains an important global cause of morbidity, mortality, and healthcare expenses.[4] A fivefold increase in incidence and a twofold increase in mortality with increasing age from 65-69 years. Excessive inflammation can cause exacerbation of lung injury, vascular leakage, and impaired oxygen exchange in the alveoli.[5,6]

The pro-inflammatory cytokines IL-1, IL-6, TNF-α, and IL-8 are released once the antigen interacts with immune system cells, activating the transcription factor NF-κB. Interleukin-8 induces the production of ROS and elastase, that damage tissue by acting as a neutrophil chemotactic agent. Through pathogen recognition (PRRs) and NF-B transcription, neutrophils activate innate immunity, which causes the proinflammatory cytokines and the expansion of other immune cells to the site of infection.[7,8]

Antioxidants such as glutathione peroxide (GPx), glutathione (GSH), and superoxide dismutase (SOD) are present in low levels and ineffective in pneumonia patients.[9,10] The production of reactive oxygen spesies (ROS) exceeds the antioxidant

capacity, potentially causing damage, which is known as oxidative stress. Increased lipid peroxidation due to ROS accumulation and oxidative stress cause elevated Malondialdehyde (MDA) levels.[7,8]

An essential nutrient called omega-3 has anti-inflammatory and antioxidant activities that are important for human health.[6,10] Specifically, peribronchial inflammation and cell death are reduced by omega-3 in terms of lung pathology.[12] Omega-3 supplementation is recognized to reduce plasma MDA levels, a marker of oxidative stress, and IL-6 levels, a marker of inflammation, in adults with CAP. Managing inflammation is necessary for avoiding the development of tissue damage and advancing clinical recovery. The purpose of this experimental research is to analyze the potency of omega-3 as an adjuvant treatment for pneumonia in reducing IL-6 levels, MDA levels, and clinical improvement duration in individuals with community-acquired pneumonia.

METHODS

This is an experimental study with pretest and posttest group design. The study sample consisted of 30 CAP patients who underwent hospitalization at Moewardi hospital in Surakarta and dr. Soehadi Prijonegoro hospital in Sragen from August – September 2022 by consecutive sampling. The inclusion criteria of the subjects of this study were age >18th years old with CAP, the PSI score was >70 or less than 70 with PDPI criteria, never taken fish capsule supplementation containing omega-3 before, and giving consent for participating in this research by signing the consent form.

Patients with community pneumonia that are in the intensive ward were excluded from this study. The other criteria that were excluded from this study ; a history of intravenous use of antibiotics and corticosteroids in the previous 90 days, comorbid or immunocompromised conditions such as HIV, malignancy, uncontrolled diabetes mellitus, post-surgery, and pregnancy. Patients using anti-coagulant drugs, in infectious diseases besides CAP, patients with autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and multiple sclerosis.

The samples devided into two groups, the control group (n=15) received standard therapy and the treatment group (n=15) received standard therapy plus omega-3 at a dose 1600mg/day. IL-6 and MDA levels were measured when the subject was admission to the hospital and there was clinical improvement. The independent variables of this study were the administration of omega 3, while the dependent variables were the IL-6 levels, MDA levels, and clinical improvement of CAP. The data was analyzed by SPSS 21 for windows.

RESULTS

The CAP patients who underwent hospitalization at Dr. Moewardi Hospital in Surakarta and Dr. Soehadi Prijonegoro Hospital in Sragen during August and September 2022 were the subjects of this experimental study. Consecutive sampling was utilized as the method of acquiring research participants. The samples were divided into 2 groups, the control group (n=15) received standard therapy and the treatment group (n=15) received standard therapy plus omega-3 at a dose 1600mg/day .

1. Characteristics of Research Subjects

The characteristics of the subjects in this study consisted of gender, age, PSI score, class of risk, and history of smoking. The research subjects in both groups were characterized to determine the homogeneity of the two groups and the viability of clinical trial procedures. The test of normality of the subject's characteristic distribution in both groups was carried out by using the Shapiro-Wilk test.

The categorical characteristic variables, including gender, class of risk, and history of smoking. There were age and PSI score for the numerical characteristic variables. The characteristics of the subjects in the form of categorical data are presented in the frequency (%), and the numerical data are presented in the mean value + standard deviation. The Homogeneity test for numerical data with normal

distribution by using independent t test, and if the data distribution is not normal, utilized Mann-Whitney test. The result of the homogeneity test with a p-value >0.05 indicated that the basic characteristics of the two groups of subjects are homogeneous.

Table one showed the results of the characteristics of the subject.

Tabel 1. Research Subject Characteristics

Characteristic	Group		p
	Control (n=15)	Omega 3 (n=15)	
Age[a]	60,33 ± 18,25	56,60 ± 17,31	0.570
Sex[b]			1.000
Male	10 (66,7%)	10 (66,7%)	
Female	5 (33,3%)	5 (33,3%)	
PSI Score[c]	82,73 ± 13,69	78,80 ± 6,95	0,519
Class of risk[c]			0.355
II	1 (3,3%)	0 (,0%)	
III	10 (66,7%)	14 (93,3%)	
IV	5 (16,7%)	1 (6,7%)	
History of smoking[c]			0.982
Passive	6 (40,0%)	6 (40,0%)	
Mild	2 (13,3%)	1 (6,7%)	
Moderate	6 (40,0%)	8 (53,3%)	
Severe	1 (6,7%)	0 (,0%)	

Information: [a] *Chi square* [b] *Independent t,* [c]*Mann-Whitney*

Based on table 1, the demographic test results showed a p-value> 0.05, indicating that the distribution of the data characteristics in the two groups of research subjects is the same (homogeneous).

2. Test Results Differences In IL-6 Levels Pretest, Posttest Between The Control Group and The Treatment Group With Omega 3.

The average pre-test (before treatment) and post-test (after treatment) IL-6 levels in the control group were 41.22 ± 43.23 and 43.92 ± 49.95. It's been reported that there was a slight increase in IL-6 post-pre treatment group, with an average increase of 2.70 ± 34.18 or 6.6%. In the Omega-3 group, the pre-test IL-6 levels obtained an average of 57.73 ± 58.63 and a post-test average of 18.20 ± 19.62. The difference in post-pre-Omega-3 IL-6 changes was found to have an average decrease of -39.53 ± 44.97 or a decrease of 68.5%.

The paired difference test (pre-post) in the control group (p = 0,140) got a p value > 0.05 and the Omega-3 group (p = 0,001) got a p value < 0.05, which means that in the control group did not experience significant changes in IL-6, meanwhile in the Omega-3 group experienced a significant decrease in IL-6. Thus, the Omega-3 supplementation was more effective in reducing IL-6 levels in patients with CAP. The unpaired difference test at the post-pre difference value (p = 0.003) with a p value <0.05 reveals it (Table 2).

Table 2. IL-6 Levels Difference Test Between Control and Omega 3 Group

IL-6	Group		p
	Control	Omega-3	
Pre test	41,22 ± 43,23	57,73 ± 58,63	0,395[a]
Post test	43,92 ± 49,95	18,20 ± 19,62	0,134[a]
p	0,140[b]	0,001*[b]	

Information: *Significant (p < 0,05); [a]*Mann-Whitney*; [b]*Wilcoxon rank test*

3. Results of The Difference in MDA Levels Pretest and Posttest Between The Control Group and The Treatment Group With Omega 3.

The MDA levels averaged 1303.58 ± 1489.17 in the pre-test control group and 1049.46 ± 1270.12 in the post-test control group. The average difference between the MDA changes in the post-pretest was found to have reduced by -254.12 ± 455.55 or -19.5%. The pre-test MDA levels in the omega-3 group averaged 1559.27 ± 1511.38 and the post-MDA levels in this group averaged 315.28±397.90. It was reported that the difference in post-pre MDA changes in the Omega-3 group had an average decrease of -1243.98 ± 1325.02 or -79.8%.

Both of the omega-3 group and the control group showed a significant decrease in MDA based on the results of the paired difference test (p=0.012 and p=0.001). Omega-3 patients lowered MDA more

than the control group did. The omega-3 therapy treatment was more effective at lowering MDA levels, according to the unpaired difference test at the post-pre difference value (p = 0.049) with p <0.05. (Table 3).

Table 3. MDA Levels Difference Test Between Control and Omega 3 Group

MDA	Group		p
	Control	Omega-3	
Pre test	1303,58 ± 1489,17	1559,27 ± 1511,38	0,885[a]
Post test	1049,46 ± 1270,12	315,28 ± 397,90	0,017[a]
p	0,012[b]	0,001*[b]	

Information: *Significant (p < 0,05); [a]*Mann-Whitney*; [b]*Wilcoxon rank test*

4. Results of The Difference in Clinical Improvement Between The Control Group and The Treatment Group With Omega 3.

The control group and the omega-3 group showed a significant decrease in MDA based on the results of the paired difference test (p=0.012 and p=0.001). Omega-3 patients lowered MDA more than the control group did. The unpaired difference test at the post-pre difference value (p = 0.049) with p<0.05 indicated that omega-3 therapy treatment was more effective in reducing MDA levels (Table 4).

Table 4. Duration of Hospitalization Difference Test Between Control and Omega 3 Group

	Group		p
	Control	Omega-3	
Clinical Improvement			0,042*
≤ 7 days	10 (66,7%)	15 (100,0%)	
> 7 days	5 (33,3%)	0 (0,0%)	

Information: *Chi square test ;* *Significant (p < 0,05)

5. The effect of Omega-3 with IL-6 levels, MDA levels, and Clinical Improvent in CAP.

The value of R for the effect of Omega-3 on the reduction IL-6 levels was 0.480, indicating a moderately significant relation between Omega-3 administration and the reduction in IL-6 (r=0.400-0.599). Despite an omega-3 supplement, it shows a significant relationship between a reduction in IL-6 levels and the value of p = 0.007 (p<0.05).

The effect of Omega-3 on the decrease in MDA levels showed a value of R= 0.459, which means the close relationship between Omega-3 administration and the reduction in IL-6 levels was in the moderate category (r=0.400 -0.599). The value of p = 0.011 (p <0.05) means that there is a significant effect of giving Omega-3 with a decrease in MDA levels (Table 5).

The effect of Omega-3 on clinical improvement reported an R-value = 0.756, which means the close relationship between Omega-3 administration and the reduction in IL-6 levels was in a strong category (r = 0.600 -0.799). The value of p=<0.001 (p<0.05) means that there is a significant effect of giving Omega-3 with accelerating clinical improvement.

Table 5. Effect of Omega-3 on the IL-6 levels, MDA levels and clinical improvement.

IV	DV	R	RC	95% CI	p-Value
Omega 3	IL-6 Levels	0,480	-42,24	-72,12 s/d -12,36	0,007*
	MDA Levels	0,459	-989,86	-1730,92 s/d -248,80	0,011*
	Clinical Improvement	0,756	-2,27	-3,03 s/d -1,51	<0,001*

Information: IV (Independent variable); DV (Dependent Variable); RC (Regretion Coefficient); *Chi square test ;* *Significant (p < 0,05)

DISCUSSION

This Purpose of this research is to determine the potency of omega-3 as an adjuvant therapy for pneumonia in reducing IL-6 levels, MDA levels, and clinical improvement duration in individuals with community-acquired pneumonia.

1. Characteristics of research subjects

This study was conducted on 30 patients who underwent hospitalization at Dr. Moewardi Hospital in Surakarta and Dr. Soehadi Prijonegoro Hospital in Sragen during August and September 2022. The samples was divided into 2 groups, control group (n=15) and Omega-3 treatmnet group (n=15). Age, gender, PSI score, history of smoking were the characteristics of the subjects in this study. There is

no significant difference in subjects characteristics between the control and Omega-3 treatment groups, that means, the patient characteristics between the control and Omega-3 treatment groups are homogeneous.

The mean age of patients in the control group in this study was 60.33 ± 18.25 years, and in the Omega-3 group it was 56.60 +17.31 years. The risk of CAP increases with age. The annual incidence of hospitalization for community pneumonia in adults aged 65 years is approximately 2000 per 100,000 population in the United States. Two percent of the older adult population is at risk for hospitalization for community pneumonia.[13]

PSI scores obtained from the control group averaged 82.73 ± 13.69 and in the Omega-3 group, the average was 78.80 ± 6.95. The PSI score is used to identify patients at risk of death and plan the patient's care for outpatient or inpatient care. The PSI score criteria include respiration rate >30 breaths/minute, PaO2/FIO2 > 250 mmHg, multilobed infiltrates on chest X-ray, systolic blood pressure <90 mmHg, and diastolic blood pressure <60 mmHg.[14,15]

This study shows the smoking history of control patients with Omega-3 treatment has almost the same proportion. Patients with a history of moderate smoking had the highest proportion, namely 6 patients (40.0%) in the control group and 8 patients (53.3%) in the Omega-3 group. A systematic review with a meta-analysis by Baskaran, V et al. 2019 shows that exposure to cigarette smoke is significantly closely related to the development of community pneumonia. Adults aged >65 years who are passive smokers also have a high risk of developing community pneumonia. Piatti et al. found that smoking modifies the epithelial surface leading to increased compliance of pneumococci compared to never-smokers. Greater bacterial attachment may lead to greater oropharyngeal colonization and therefore a greater risk of developing community pneumonia.[16]

2. Effect of Omega 3 on the IL-6 Levels in Community-Acquired Pneumonia

The difference between post and pretest levels of IL-6 in the Omega-3 group decreased by 68.5%. The relationship between Omega-3 administration and IL-6 reduction in this study was in the moderate category, which means that Omega-3 treatment was able to reduce IL-6 levels more than patients without Omega-3 supplementary therapy. The addition of Omega-3 therapy has an effect in reducing IL-6 levels compared to standard therapy in patients with CAP. The study by Zhou et al., 2021 stated that IL-6 levels were normal at levels <10 pg/ml. Another study, according to Liu et al., 2020 stated that IL-6 >32.1 pg/ml had a risk for severe complications. Several healthy individuals were observed to have IL-6 levels of 43.5 pg/ml. In this study, IL-6 levels after omega-3 administration had decreased significantly, but had not reached normal levels as healthy people in general, but could decrease at IL-6 levels <32.1 so that the risk for severe complications could be reduced.[16.17]

Interleukin-6 is a pleiotropic cytokine that plays an important role in transmitting defense signals from invading pathogens or against tissue damage to stimulate acute-phase reactions, immune responses, hematopoiesis, and various internal organs as host defense. IL-6 is a protein secreted by 26-kD, a soluble protein produced by T cells and activates B cell differentiation to produce antibodies. The pathophysiology of CAP in the early stages is associated with proinflammatory cytokines produced by alveolar macrophages, particularly IL-6 and tumor necrosis factor-α, where IL-6 levels are significantly elevated in conditions of pulmonary consolidation, hypoxia, and shock. Several studies have suggested that IL-6 can be used as an independent predictor of CAP mortality. This is based on findings showing a positive correlation between serum IL-6 concentrations and recent mortality in community pneumonia.[18,19,20]

Omega-3 plays an important role as an anti-inflammatory resulting from PPAR-γ activation and reduces cytokine production. Research by Eftekhari, et al stated that Omega-3 supplementation can

reduce levels of hs-CRP and IL-6. In line with research by Prasetyo in 2015, said that the administration of Omega-3 significantly reduced IL-6 levels in pneumonia patients.[21,22,23]

3. Effect of Omega 3 on the MDA Levels in Community-Acquired Pneumonia

The treatment group's administration omega-3 supplements reduced significantly. In this group, the difference in the MDA levels between the pretest and posttest was 79.8%. The administration of omega-3 was able to lower MDA levels compared with patients without receiving omega-3 therapy because of the strong links between the treatment of omega-3 and the lowering in IL-6, which was in the moderate range.

Malondialdehyde could be utilized as a biomarker of oxidative stress though it is a stable end product of the process that leads to a rise in lipid peroxidation during oxidative stress. Based on the recent research in 2021 by Pinar Koyuncu et al, patients with CAP showed higher levels of MDA in their pleural fluid than individuals who had cancer and heart failure.[24,25,26]

Research by Kesavuluet al. revealed a significant correlation between Omega-3 supplementation and a reduction in MDA levels. According to Heshmati et alsystematic .'s review and meta-analysis, omega-3 n-3 PUFA supplementation could reduce plasma MDA levels in both young and old persons. By enhancing the host's nonspecific and specific immune responses, Omega-3 treatment has a positive impact on acute pneumonia, according to experimental studies on the subject conducted by Sharafi et al. in 2013 using experimental animals.[27,28]

There isn't presently a value for MDA's normal value that can be used as a baseline. Age and the activity of enzymes like glutathione peroxidase, catalase, and superoxide dismutase can as antioxidants have an impact on MDA levels. MDA levels could also be impacted by environmental factors like pollution and disease-related antioxidant medicines. MDA levels are a specific indicator of oxidative stress in each disease. According to Dixon et al1998 .'s study, plasma MDA levels in healthy individuals ranged between 0.1 and 1.17 nmol/mL, whereas Suhartika et al research .'s in 2020 indicates that these levels were 3.01 nmol/m.[29,30,31] In this study, an ELISA kit with ng/ml units and a detection range of 31.25–2000 ng/ml was employed. No study divides up typical MDA concentrations into ng/ml categories.

4. Effect of Omega 3 on Clinical Improvement in Community-Acquired Pneumonia

Clinical improvements were seen in all patients 7 days after receiving Omega-3 supplements for community pneumonia. This reveals that giving patients additional Omega-3 therapy decreases the time they need to take medication for CAP. Clinical improvements can come earlier with Omega-3 therapy than without it.

According to Hinojosa's research, 2020, supplementation of omega-3 fatty acids for two months boosted animal stability, reduced bacteremia, and reduced lung pathology, particularly peribronchial inflammation and cell death. It is interpreted that omega-3 fatty acids have anti-inflammatory activity in pneumococcal pneumonia. Oral supplementation with omega-3 fatty acids showed a protective impact due to its being linked to fewer immune cell infiltrates and pneumonia consolidation based on pulmonary histopathology.[12]

CONCLUSION

Omega-3 supplementation as adjuvant therapy at a dose of 1600 mg/day can reduce IL-6 and MDA levels associated with the duration of clinical improvement in community acquired pneumonia.

REFERENCES

1. Koul P, Chaudhari S, Chokhani R, Christopher D, Dhar R, Doshi K, et al. Pneumococcal disease burden from an Indian perspective: need for its prevention in pulmonology practice. Ind Chest Soc. 2019;36(3):216-25.

2. Tejada S, Romero A, Rello J. Community-acquired pneumonia in adults: what's new focusing on epidemiology, microorganisms and diagnosis?. Erciyes Med J. 2018;10(4):177-82.
3. Talwar D, Sharma RK. Epidemiology and risk factors of pneumonia. In: Jindal SK, Chetambath R, editors. World clinic pulmonary & critical care medicine pneumonia. New Delhi: JP Medical Ltd.; 2019. p. 1-11.
4. Cillóniz C, Cardozo C, García C. Epidemiology, pathophysiology, and microbiology of community acquired pneumonia. Ann Res Hosp. 2018;2(1):1-8.
5. Endeman H, Meijvis SCA, Rijkers GT, Van Velzen-Blad H, Van Moorsel CHM, Grutters JC, et al. Systemic cytokine response in patients with community-acquired pneumonia. Eur Respir J. 2011;37(6):1431-8.
6. Gammone MA, Riccioni G, Parrinello G, D'Orazio N. Omega-3 polyunsaturated fatty acids: benefits and endpoints in sport. Nutrients. 2019;11(1):46-62.
7. Castillo RL, Carrasco RA, Álvarez PI, Ruiz M, Luchsinger V, Zunino E, et al. Relationship between severity of adult community-acquired pneumonia and impairment of the antioxidant defense system. Biol Res. 2013;46(2):207-13.
8. Mao C, Yuan JQ, Lv Y Bin, Gao X, Yin ZX, Kraus VB, et al. Associations between superoxide dismutase, malondialdehyde and all-cause mortality in older adults: A community-based cohort study. BMC Geriatr. 2019;19(1):1-9.
9. Xu W, Zhao T, Xiao H. The implication of oxidative stress and AMPK-Nrf2 antioxidative signaling in pneumonia pathogenesis. Frontiers in Endocrinology. 2020;400(11):1-12.
10. Ghadiri M, Yung EY, Haghi M. Role of oxidative stress in complexity of respiratory diseases. In: Maurya PK, Dua K, editors. Role of oxidative stress in pathophysiology of diseases. 1st ed. Singapore: Springer; 2020. p. 67-92.
11. Ishihara T, Yoshida M, Arita M. Omega-3 fatty acid-derived mediators that control inflammation and tissue homeostasis. Int Immunol. 2019;31:559-67.
12. Hinojosa CA, Gonzalez-Juarbe N, Rahman MM, Fernandes G, Orihuela CJ, Restrepo MI. Omega-3 fatty acids in contrast to omega-6 protect against pneumococcal pneumonia. Microb Pathog. 2020;141:1-11.
13. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. Clin Infect Dis. 2017;65(11):1806-12.
14. Soepandi PZ, Burhan E, Nawas A, Giriputro S, Isbaniah F, Agustin H, et al. Pneumonia komunitas. In: Soepandi PZ, Burhan E, Nawas A, Giriputro S, Isbaniah F, Agustin H, et al, editors. Pneumonia komunitas pedoman diagnosis dan penatalaksanaan di Indonesia. 2nd ed. Jakarta: Badan Penerbit FKUI; 2014. p. 3-37.
15. Satici C, Demirkol MA, Sargin Altunok E, Gursoy B, Alkan M, Kamat S, et al. Performance of pneumonia severity index and CURB-65 in predicting 30-day mortality in patients with COVID-19. Int J Infect Dis. 2020;98:84–9.
16. Zhou J, He W, Liang J, Wang L, Yu X, Bao M, et al. Association of interleukin-6 level with morbidity and mortality in patients with coronavirus disease 2019 (COVID-19). Jpn J Infect Dis. 2021;74(4):293-98.
17. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, c-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020;127(6):1-5.
18. Khattab AA, El-Mekkawy MS, Shehata AM, Whdan NA. Clinical study of serum interleukin-6 in children with community-acquired pneumonia. Egypt Pediatr Assoc Gaz. 2018;66(2):43-8.
19. Andrijevic I, Matijasevic J, Andrijevic L, Kovacevic T, Zaric B. Interleukin-6 and procalcitonin as biomarkers in mortality prediction of hospitalized patients with community acquired pneumonia. Ann Thorac Med. 2014;9(3):162-7.
20. Yudhawati R, Yuniawati E. Correlation of serum interleukin-6 level and pneumonia severity index score in patient with community-acquired pneumonia. J Adv Pharm Educ Res. 2021;11(3):58-62.

21. Faizah AK, Kresnamurti A. Evaluation of Antiinflammatory Activity of Marine Omega-3 in Rats. Indones J Pharm Clin Res. 2020;2(2):1-5.
22. Calder PC. Omega-3 Fatty Acids and Inflammatory Processes. Nutrients. 2010;2(3):355-74.
23. Prasetyo SE. Pengaruh Omega-3 fatty acid terhadap kadar interleukin 6 dan perbaikan klinis pada pasien pneumonia komunitas. Universitas Negeri Sebelas Maret; 2015.
24. Cui X, Gong J, Han H, He L, Teng Y, Tetley T, et al. Relationship between free and total malondialdehyde, a well-established marker of oxidative stress, in various types of human biospecimens. J Thorac Dis. 2018;10(5):3088-197.
25. Parwata MOA. Antioksidan. In: Parwata MOA, editor. Bahan Ajar Uji Bioaktivitas : Antioksidan. 1st ed. Bali: Univ Udayana; 2009. p. 12-37.
26. Koyuncu P, koyuncu A, Ulkar SE. Evaluation of nitric oxide metabolism and malondialdehyde levels as an indicator of oxidant stress in malign and parapneumonic pleural effusion. J Surg Med. 2021;5(3):311-4.
27. Sharma S, Chhibber S, Mohan H. Dietary supplementation with omega-3 polyunsaturated fatty acids ameliorates acute pneumonia induced by Klebsiella pneumoniae in BALB/c mice. Can J Microbiol. 2013;59(7):503-10.
28. Lima Rocha JÉ, Mendes Furtado M, Mello Neto RS, da Silva Mendes AV, Brito AK da S, Sena de Almeida JOC, et al. Effects of Fish Oil Supplementation on Oxidative Stress Biomarkers and Liver Damage in Hypercholesterolemic Rats. Nutrients. 2022;14(3):1-15.
29. Karatas F, Karatepe M, Baysar A. Determination of free malondialdehyde in human serum by high-performance liquid chromatography. Analitycal Biochemistry. 2002;311:76-79.
30. Dixon ZR, Shie FS, Warden B, Burri B, Neidlinger TR. The effect of low carotenoid diet on malondialdehyde-thiobarbituric acid (MDA-TBA) concentrations in women: a placebo-controled double blind study. J AM Coll. Nutr. 1998;62:149-50.
31. Suhartika E, Amir Z, Sinaga BYM, Eyanoer PC. Perbedaan kadar malondialdehid (MDA) dalam darah pasien tuberculosis paru dengan penyakit diabetes mellitus, tuberculosis paru tanpa diabetes mellitus dan orang sehat di Medan. J Respir Indo. 2020;40(4):219-24.

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