Research Paper

International Journal of Research and Review
Vol. 10; Issue: 10; October 2023
Website: www.ijrrjournal.com
E-ISSN: 2349-9788; P-ISSN: 2454-2237

The Effect of High Fat Formula Liquid Feeding on the Value of PCO_2 and Duration of Use of Respiratory Aids for COVID-19 Patients with Critical Illness

Dewi Susanti Febri[1,2], Gestina Aliska[3,4], Afriani Afriani[5,6], Nisnawati[7], Azzah Saniyyah[8]

[1] Department of Clinical Nutrition, M Djamil General Hospital, Padang, Indonesia
[2] Department of Nutrition, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[3] Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[4] Department of Clinical Pharmacology, M Djamil General Hospital, Padang Indonesia
[5] Department of Pulmonology and Respiratory, M Djamil General Hospital, Padang, Indonesia
[6] Department of Pulmonology and Respiratory, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[7] Nutrition Instalation, M Djamil General Hospital, Padang, Indonesia
[8] Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

Corresponding Author: Dewi Susanti Febri (dewisfjambi@yahoo.com)

DOI: https://doi.org/10.52403/ijrr.20231035

ABSTRACT

Background: In December 2019, WHO announced the outbreak of COVID-19 disease caused by SARSCOV2. COVID-19 is a global pandemic characterized by high morbidity and mortality. SARS-CoV2 with there are many symptoms, about 20-26% of patients with COVID-19 pneumonia become severe or critical, requiring hospitalization for respiratory support. In Indonesia, COVID-19 has been increasing since 2020, and on February 2021, the Covid-19.go.id page had 1.157.837 confirmed cases, 176.291 active cases, 949.990 recovered, and 31.556 death cases. Acute respiratory complications requiring treatment in the intensive care unit are the main cause of high morbidity and mortality in patients with COVID-19. Nutrition therapy has influenced for outcomes of COVID-19 patients.
Methods: The primary purpose of this study was to compare the value of PCO2, and duration of use of respiratory support for COVID-19 patients with critical illness. The result compared the COVID-19 patients who had been administered with high lipid formula nutrition (PULMOSOL) and patients who had been administered with standard liquid formula nutrition. The rate of the intervention group that experienced an increase in PCO2 was 55.6%, higher than those who experienced a decrease in PCO2 (50%).
Results: Based on the analysis results, there was no difference in the administration of PULMOSOL and standard formula based on PCO2 in the use of ventilators in COVID-19 critically ill patients in Dr. M Djamil Padang General Hospital ($p>0.05$) with HR = 1.39 (95% CI 1.55-3.55). In patients with increased PCO2, it was found that the intervention group who died was 55.6%, lower compared to the control group (62.5%). The same in patients with decreased pCO2, group the intervention group who died was 50.0%, higher than the control group (40%).
Conclusion: Statistical tests demonstrated there was no relationship between the administration of PULMOSOL and the outcome of critically ill COVID-19 ($p>0.05$).

Keywords: Covid-19, critically ill, nutrition, high lipid formula

INTRODUCTION

In December 2019, the World Health Organization (WHO) announced some cases of pneumonia that occurred in Wuhan, China. Those pneumonias spread by the

SARS-CoV2 virus, causing the COVID-19, stands for coronavirus disease. As a result of being infected with SARS-CoV2, various conditions may occur, from asymptomatic symptoms to severe symptoms or even death. COVID-19 patients with severe conditions are treated intensively as critically ill patients. COVID-19 entered Indonesia on March 2nd, 2020, with 2 cases. Up to February 2021, according to the Covid-19.go.id page, there were 1.157.837 confirmed cases, 176.291 active cases, 949.990 recovered, and 31.556 death cases. Based on the most recent epidemiological studies available, there are specific risk factors for severe COVID-19 infection (hospitalization, intensive care unit [ICU] admission, mechanical ventilation, or death).[1]

Acute respiratory complications requiring management in the ICU are the leading cause of high morbidity and mortality in patients with COVID-19. It was most commonly found in the elderly and patients with compromised immune systems, polymorbidity, or malnutrition. COVID-19 patients who undergo prolonged treatment in the ICU can directly worsen nutrition or lead to malnutrition through loss of skeletal muscle mass and function resulting in disability and worsening quality of life. Therefore, prevention, diagnosis, and treatment of malnutrition should be routinely performed in the management of COVID-19 patients. *European Society for Clinical Nutrition and Metabolism* (ESPEN) provides a practical guide for the nutritional management of COVID-19 patients focuses on those in ICU or older and multimorbid patients, with regard to malnutrition and its negative impact on patient survival.[2]

Elderly and polymorbid individuals infected by SARS-COV-2 must be checked for their malnutrition status through screening and assessment. Identification of risk and the presence of malnutrition should be the initial step in the general assessment of all patients regarding their higher risk categories, such as the elderly and individuals with chronic and acute conditions. Because the identification of malnutrition risk is not just defined by low body mass, but also the body's inability to maintain healthy skeletal muscle mass and composition, obese patients should be screened and examined based on the same criteria.[3]

GLIM or *Global Leadership Initiative on Malnutrition* criteria have been introduced by the Association of Clinical Nutritionists to diagnose malnutrition. GLIM proposes a two-step approach to diagnosing malnutrition: initial screening to determine “at risk” status using a validated screening tool, such as MUST or NRS-2002; and second is to assess the diagnosis and severity of malnutrition. According to GLIM, a diagnosis of malnutrition requires at least 1 phenotypic criterion and 1 etiological criterion. The above considerations appear to fully apply to patients at risk of severe SARS-CoV-2 infection or hospitalization with COVID-19 infection, given that patients with COVID-19 are more likely to be malnourished. The most commonly reported condition is worsening of the disease (such as the elderly and people with comorbidities). Maintaining nutritional status and preventing or treating malnutrition also has significant potential to reduce complications and negative outcomes in malnourished patients who may get COVID-19 in the future.[3]

During virus pandemics in the future, we may face a “double burden” of malnutrition: undernourishment and overnutrition will increase the disease severity. Obesity increases the risk of hospitalization and death from influenza virus infection because obesity inhibits virus-specific CD8 T-cell responses and antibody responses to influenza vaccines. The challenge of future viral pandemics is not only to protect those affected by malnutrition but also those with obesity. Energy requirements can be assessed using indirect calorimetry if a sterility measurement system is safely available or by weight-based prediction equations/formulas: 27 kcal per kg body weight/day; total energy expenditure for poly morbid patients aged > 65 years 30 kcal per kg body weight/day;

total energy expenditure for poly morbid patients with very low body weight
30 kcal per kg body weight/day; guide values for energy intake in the elderly. This value must be adjusted individually by considering the nutritional status, level of physical activity, disease status, and tolerance
*The target of 30 kcal/kg body weight in very underweight patients should be achieved carefully and gradually, as this is a population at high risk for suffering from *refeeding syndrome*. [3]
Protein requirements are usually estimated using a formula such as:
(1) 1 g protein per kg body weight/day in the elderly; the amount must be adjusted accordingly individually with attention to nutritional status, level of physical activity, disease status, and tolerance (Recommendation 2 in reference).
(2) 1 g protein per kg body weight/day in poly morbid inpatients to prevent weight loss, reduce the risk of complications and re-hospitalization and improve functional *outcomes* (Recommendation 5.1 in Ref). [2]
Lei Zhang and Yunhui proposed recently that vitamin A, vitamin D, vitamin B, vitamin C, omega-3 polyunsaturated fatty acids, selenium, zinc, and iron, should be considered in the COVID-19 patient's micronutrient *assessment*. Although it is important to prevent and treat deficiency micronutrients, there is no definite evidence that the use of micronutrients supraphysiological or supratherapeutic routinely and empirically can prevent or improve the clinical outcome of COVID-19. [4,5]

Oral nutritional supplements (ONS) must provide at least 400 kcal/day including 30 g protein/day or more and should be continued for at least one month. The effectiveness and expected benefits of ONS will be evaluated once a month. Patients infected with SARS-CoV-2 outside the ICU need treatment to prevent or correct nutritional deficiencies. Nutritional treatment should begin earlier during hospitalization (within 24-48 hours). Nutritional status may be disrupted, especially in elderly patients and patients with multiple comorbidities, and treatment and nutritional goals must be achieved gradually to avoid refeeding syndrome. Enteral nutrition (EN) should be an option when nutritional requirements cannot be met by the oral route, for example, when oral intake is not thought to be possible performed for more than three days or it is estimated that there are less than half of the need's energy for more than one week. In these cases, EN may be preferable to parenteral nutrition (PN), due to the lower risk of both infectious and non-infectious complications. Monitoring for potential complications of EN should be conducted.[2]
Reeves et al. also reported that protein-energy intake in ARDS patients who were treated with NIV was inadequate. It is supposed to be shown that airway complications may occur with a longer duration of median non-invasive ventilation in these NIV patients treated with enteral feeding. The recommendation to start enteral feeding may be interrupted by nasogastric tube (NGT) placement, leading to 1) air leaks that may reduce the effectiveness of NIV; 2) gastric dilatation may affect diaphragmatic activity and the effectiveness of NIV. The observations above explained nutritional implementation partly. Severely inadequate enteral feeding might result in the patient being starving, especially within the first 48 hours of ICU stay, and a higher risk of malnutrition and related complications. Therefore, peripheral parenteral nutrition might be considered in this condition.[6]
Patients who are supplemented with oxygen via nasal cannula are usually considered medically suitable to continue oral medication. Several studies have described the implementation of nutritional support using this technique. However, there is little evidence to suggest that calorie and protein intake may remain low and inadequate to prevent or treat malnutrition in patients with HFNC, and they have unpublished data. Ignoring the adequate calorie-protein provision may worsen nutritional status and related complications. An adequate rating regarding nutritional intake is recommended

by administering oral nutritional supplements or by enteral nutrition if the oral route is inadequate. Production of carbon dioxide in critically ill patients treated in the ICU can be affected by the composition of the nutrients given, either enteral or parenteral, and these conditions will affect the weaning process. Respiratory failure is precipitated by a high intake of carbohydrates because carbohydrates have RQ=1, which this respiratory quotient represents 1 part of carbohydrate that produces 1 part carbon dioxide. A study by Faramawy et al., in 2014 demonstrated that high-fat diets reduced the need for ventilator breathing assistance and reduced the length of duration in using a mechanical ventilator. This study was conducted on 100 patients diagnosed with type II respiratory failure, divided into 2 groups: group A as control and group B for the treatment with high-fat low carb nutrition. It was statistically very significant for the duration of using mechanical ventilators between the treatment group less than 62 hours compared to the control group, as well as improvements in PCO2 in the treatment group.[7]

The long-term prognosis of intensive care unit survivors is influenced by the physical, cognitive, and psychiatric disorders that occur after their stay in ICU. Loss of skeletal muscle mass and function can be significant and is a major problem in intensive care patients. This may mainly occur in elderly and more susceptible comorbid patients with pre-existing catabolic states and impaired skeletal muscle mass and function; besides, the group of these patients may be more likely to elicit a more intense catabolic response due to COVID-19 and general ICU conditions. Long duration of ICU stay above two weeks for most predisposed COVID-19 patients may increase muscle catabolism. Providing the right energy and providing the right protein amount adequately are essential to prevent loss of muscle mass and further impairment of function.[6,7]

Intervention and nutritional therapy need to be considered as an integral part of the approach of SARS-CoV-2 patients in the ICU. At every step of treatment, nutritional therapy should be part of patient care, especially for elderly, frail individuals, and patients with a history of comorbidities.

MATERIALS & METHODS

Study Design

This study was a randomized clinical trial to compare the COVID-19 patients who were administered high lipid formula nutrition with standard liquid formula nutrition. This study was conducted in Dr. M. Djamil General Hospital from March 2021 until September 2021. The clinical outcomes were intrahospital mortality, PCO2 value, and time of conversion of mechanical ventilator to respiratory aids.

Study Population and Sample

Patients aged over 18 years with a confirmed diagnosis of COVID-19 and NG tube installed, treated in red zone HCU and ICU at M. Djamil Hospital, on HFNC or mechanical ventilator installed were included in this study. On the other hand, patients with severe renal impairment with creatinine clearance < 30 mg/min, patients who died before 7 days of treatment, and patients whose NGT could not be used because the residue was more than 500 ml per 6 hours or was present severe stress ulcers or patients with allergies to liquid food components (such as diarrhoea) were excluded. The sample size was determined using an observational study formula with one study population. In the end, it was obtained 26 patients as minimal samples and we determined 30 patients per group.

Data Collection

Initial investigations included a complete blood count, inflammation marker and serum biochemical test (including renal function and liver function). Nasal and pharyngeal swabs were tested for SARS-CoV using real-time RT-PCR assays approved by the Food and Drug Authorization. The data were collected from medical records of all confirmed COVID-19 patients with critical illness who were hospitalized in the ICU Red zone at Dr. M. Djamil General Hospital. The data collected in medical records include demography data (name, age, sex,), laboratory test results, diagnosis, and treatment. PCO2 values were collected from the laboratory. The clinical outcomes were analyzed from daily follow-up data of patients.

STATISTICAL ANALYSIS

Basic characteristic data was presented using descriptive statistics with a nonpaired T-test. The results were considered statistically significant if $p < 0.05$. Collected quantitative data were processed and analyzed by computerization. This study has been by the Research Ethics Committee of M.Djamil General Hospital with Number: 123/KEPK/2021.

RESULT

Data were obtained from medical records of all confirmed COVID-19 patients with critical illness who were hospitalized in the ICU Red zone at Dr. M. Djamil General Hospital. We had 36 patients who were investigated according to inclusion and exclusion criteria. Because the number of samples fulfilled was less than the minimum sample required, we conducted an interim analysis to justify whether the 19 data was feasible for analysis. Based on the results of an interim analysis with two analysis techniques, which were *Pocock* and *O'Brien-Fleming*, we obtained a significance value of less than 0.05 in two scenarios. Scenario one, namely in the number of samples that were fulfilled 19 and scenario two which was the final scenario where the number of samples was fulfilled at least 30 obtained a P value of 0.05. This demonstrated that if you stop or stop the rule of data collection in scenario one and continue in scenario two, you will get the same analysis results. If the sample was still filled up to a minimum sample of 30 or even more than a sample of 30, the results of the analysis remained consistent with the results of the hypothesis analysis that would be conducted in scenario one.

Patients included in this study were 16 males (44.4%), 20 females (55.6%), and most (58.3%) aged more than 60 years old. Twenty-two patients or more than half of patients (61%) were obese with a BMI of more than 24.9 kg/m^2. Mortality was a little higher (58.8%) in the intervention group than in the control group (52.6%). Length of stay (LOS) was longer in the intervention group than control group. Death as the final stage of treatment was the most frequent outcome and was shown to be the same in amount, both in the intervention group and control group (See Table 1).

From laboratory results, all of the patients showed hypoalbuminemia and increased markers of inflammation such as D-Dimer, IL-6, and CRP. All of the patients with increasing levels of D-Dimer than normal had mortality outcomes of 55.6%. Systematic review and meta-analysis from 100 records with D-Dimer reported initial. D-Dimer as a significant association risk for severity of disease and mortality outcomes.

Table 1. Characteristics of Patients

Variables	All patients (n=36)	High lipid formula (n=17)	Standard formula (n=19)	P value
Sex				0.103
Male (n,%)	16 (44.4%)	5 (29.4%)	11 (57.9%)	
Female (n,%)	20 (55.6%)	12 (70.6%)	8 (42.1%)	
Age				0.686
18-60 (n,%)	15 (41.7%)	7 (41.2%)	8 (42.1%)	
> 60 (n,%)	21 (58.3%)	10 (58.8%)	11 (57.9%)	
BMI				
<18.5	1/36	1/17	0/19	
18.5-22.9	5/36	2/17	3/19	
23-24.9	8/36	3/17	5/19	
>24.9	22/36	11/17	11/19	
Outcome				0.744
Mortality	20 (55.6%)	10 (58.8%)	10 (52.6%)	
Length of stay (n,%)	8.94 + 3.439	9.88 + 3.140	9.00 + 3.771	0.927

Table 2. Laboratory Data

	All patients (n=36)	High lipid formula (n=17)	Standard formula (n=19)	P value
Hb	12.600 + 2.4871	12.918 + 2.1944	12.316 + 2.7508	0.327
Albumin	3.100 (0.4 – 3.9)	3.153 – 0.3165	3.000 (0.4-3.6)	0.116
ALT	49.00 (14-167)	70.76 – 41.230	40.50 (14-137)	0.126
AST	43.00 (15-259)	45.00 (15-151)	40.50 (15-259)	0.822
Ureum	45.00 (18-112)	44.47 – 18.618	45.00 (18-112)	0.708
Creatinine	0.800 (0.5-49.0)	0.800 (0.6-1.4)	0.800 (0.5-49.0)	0.644
pH	7.45000 (2.383-7.601)	7.41500 (2.383-7561)	7.46900 (6.870-7601)	0.118
PCO2	36.350 (24.6-230.7)	39.959 – 12.5230	36.00 (29.0-103.0)	0.558
PaO2	68.050 (22.6-230.7)	65.000 (22.6-230.7)	72.400 (32.0-187.0)	0.845
HCO3-	24.700 (2.1-36.5)	24.500 – 3.6907	25.000 (21-36.5)	0.313
BE	0.800 (-45.0 – 26.4)	(-0.329 – 4.0359)	3.000 (-450 – 26.4)	0.026
Sodium	136.67 (98-154)	138.00 (112-143)	135.00 (98-154)	0.221
Potassium	3.800 (0.8-7.9)	3.700 (0.8 – 4.7)	3.900 (2.8-7.9)	0.374
Calcium	8.450 (0.6-98)	8.250 (0.6-9.8)	8.750 (4.8-9.6)	0.369
Blood glucose	224.68 + 71.096	224.94 + 65.209	224.41 + 78.568	0.8
IL-6	48.400 (5.2-860.6)	31.500 (5.2 – 562.0)	293.360 – 359.9677	0.208
D-dimer	2693.00 (10-710000)	2693.00 (608-9906)	2682.00 (10-710000)	0.46
CRP	106.30 – 52.736	94.86 – 54.162	160.00 (76-160)	0.183
Procalcitonin	0.9050 (0.05-9.69)	0.9500 (0.14-969)	0.8600 (0.05-7.96)	0.91

Table 3. Survival Analysis of PULMOSOL Administration and Standard Formula based on pCO2 in the Use of Ventilators in Critically Ill COVID-19 Patients at Dr. M. Djamil Padang General Hospital

Group	pCO2	Rate (%)	Mean survival (95% CI)	p-value	R (95% CI)
Intervention	Increased	55.6	7 (6-8)	0.485	1.39 (0.55-3.55)
	Decreased	50	7 (5-11)		
Control	Increased	62.5	8 (5-12)		
	Decreased	40	8 (5-11		

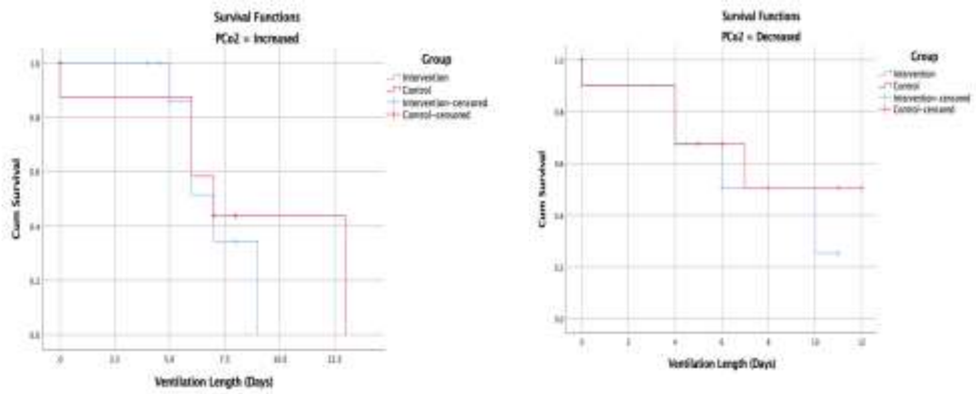

Figure 1: (a) PCO2 increased (b) PCO2 decreased

Several studies have reported increased D-dimer levels to be positively associated with disease severity, composite outcomes, and high mortality in Covid-19. (See table 2).

The rate of the intervention group that experienced an increase in PCO2 was 55.6%, higher than those who experienced a decrease in PCO2 (50%). There was no difference in the length of treatment between those who experienced the increase or decrease in PCO2, which was 7 days for each. Based on the analysis results, there was no difference in the administration of PULMOSOL and Cox-regression standard formula based on PCO2 in the use of ventilators in COVID-19 critically ill patients in Dr. M Djamil Padang General Hospital ($p>0.05$) with HR = 1.39 (95% CI 1.55-3.55). (See Table 3 and Figure 1)

In patients with increased PCO2, it was found that the intervention group who died was 55.6%, lower compared to the control group (62.5%). The same in patients with decreased pCO2, group the intervention group who died was 50.0%, higher than the control group (40%). Statistical tests demonstrated there was no relationship between the administration of PULMOSOL and the outcome of critically ill COVID-19 ($p>0.05$). (See Table 4)

Table 4. Relationship between PULMOSOL administration and COVID-19 Critically Illness Patient outcomes based on pCO2 Value

Outcomes	**PCO2 increased**			
	Group		p-value	OR (95% CI)
	Intervention (f/%)	Control (f/%)		
Died	5 (55.6)	5 (62.5)	1.000	0.78 (0.11-5.24)
Alive	4 (44.4)	3 (37.5)		Ref
Outcomes	PCO2 decreased			
	Group		p-value	OR (95% CI)
	Intervention (f/%)	Control (f/%)		
Died	5 (50.0)	4 (40.0)	1.000	1.51 (0.26-8.82)
Alive	5 (50.0)	6 (60.0)		Ref

DISCUSSION

In this study, the number of samples was less than the minimum sample required (30 samples), researchers only managed to find 19 samples. Based on the results of the interim analysis with two analysis techniques, Pocock and *O'Brien-Fleming*, a significance value less than 0.05 was obtained in two scenarios. In the 1st scenario, the number of samples is 19 and in the 2nd scenario, the number of samples at least 30. So if this study is stopped in 1st scenario and continued in 2nd scenario, the results of the analysis will be the same. This is evidenced by the interemalysis graph that there is a decrease in the curve, it means that in samples of less than twenty or even hundreds there will be a decrease.

Based on Table 1, it is known that more patients are female, elderly (> 60 years), and obese. It is known that female COVID 19 patients with diabetes have a higher risk of ICU admission in the study of Lukas et al's (women (OR 2.00), men (OR 1.39).[8] Obesity, diabetes and hypertension are more common in women. Independently, diabetes, chronic kidney disease, increased ratio of neutrophil to lymphocyte, and ferritin predicted mortality in women.[9] The category of patient in this study were mostly over than 60 years old (58.3%), the higher the age than the less muscle mass. Study of Fabyan Esberard et al showed that muscle area (MA) < 92 cm^2 (OR= 7.94; $P < 0.005$) was an independent risk factor for mortality in hospitalized patients with moderate to severe COVID-19.[10]

The patients were mostly obese (61%), based on previous meta-analysis, it was found that there was a relationship between class III obesity (BMI $\geq$ 40 kg/m^2), with mortality and with respiratory tube requirement in COVID-19 patients.[11] Visceral fat deposits are associated with COVID-19 severity levels. Angiotensin-converting enzyme-2 (ACE-2) is a receptor for severe SARS-CoV-2 infection, which is expressed in many tissues including white adipose tissue, where ACE-2 expression is higher in patients with comorbid obesity. [12]

In addition to the elderly and obesity mentioned above, there are patient characteristics that also influence adverse outcomes in this study, including the presence of comorbid diabetes mellitus type 2, an initial condition with severe respiratory distress, increased inflammatory markers (Table 1) and mechanical ventilator requirement due to respiratory failure.[13]

Based on Table 2, there is no difference between the administration of PULMOSOL and the standard formula based on PCO2. And based on the results of statistical tests in Table 3, there is no relationship between PULMOSOL administration and patient outcomes ($p>0.05$). Macronutrient ratios are important in the nutritional feeding of the patients with acute respiratory failure. Enteral nutrition with a higher fat content (up to 55%) and lower carbohydrate content (about 28%) is more appropriate in hypercapnic respiratory failure, such as hypoventilation syndrome in obesity, chronic bronchitis, emphysema and neuromuscular disorders. This refers to the theory that complete burning of fat produces less carbon dioxide than burning carbohydrates or protein, therefore, a high-fat and low-carb diet decreased CO2 production and ventilation periods while increasing O2 consumption and mechanical ventilation.[14].

Mahdieh et al (2022) examined the effect of PCO2 levels in patients with acute respiratory failure who were mechanically ventilated, that given a fat-based formula for 14 days. As a result, PCO2 decreased significantly in the group that was given a fat-based formula of the mixture of olive oil and sunflower oil (composition: 20% protein, 45% olive oil and sunflower oil, 35% carbohydrates), while in the control group (composition: 20% protein, 30% fat, 50% carbohydrate), and the group with sunflower oil-based formula only (composition: 20% protein, 45% sunflower oil, 35% carbohydrates) have no beneficial effect. In addition to PCO2, in the group that was given a mixture of olive oil and sunflower oil, there were other beneficial effects such as eight times faster separation time from mechanical ventilation, significantly decreased serum CRP levels, and also increased serum antioxidant concentrations. [14]

Olive oil provides benefits through its contribution of a high proportion of oleic acid. Other components, including plant sterols, tocopherols and polyphenols, also have beneficial effects. In this study, there was a significant reduction in arterial CO2 pressure in the group that given high-fat nutrition with olive oil. However, this study also had limitations, in a small population (93 patients), short-term intervention and follow-up and was not a commercial formula (formulated by hospital kitchen). [14]

Faramawy et al (2014) examined that providing EN with high-fat and low-carbohydrate foods in patients with type 2 respiratory failure, where 50 patients received food with standard calories (53.3% carbohydrates, 30% fat, and 16.7% protein), and 50 patients in the treatment group (28.1% carbohydrates, 55.2% fat, and 16.7% protein). The treatment group experienced a 16% reduction in arterial PCO2, an 8% reduction in weaning volume, and spent an average of 62 hours less on mechanical ventilation. In Faramawy's study, the standard foods provided were according to WHO 1998, while the high-fat foods were prepared by the hospital with a total daily calorie of 3000 kcal.[7]

N-3 polyunsaturated fatty acids or N-3 PUFA include α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). EPA and DHA are obtained from fish oil and ALA is obtained from flax seeds, walnuts, turnips, and quinoa. N-3 PUFA may affect viral replication and reduce inflammatory reactions in critical COVID-19 patients.[15]

In viral replication, N-3 PUFAs generally modulates changes in membrane composition, changes enzyme activity, and modifies membrane ion transport. Several studies have shown that N-3 PUFA significantly reduces the concentration of n-SREBP (a gene that has an effect on viral transcription). The effect of N-3 PUFA on inflammation is that it can compete with arachidonic acid (ARA) to become a preferential substrate, so that resulting less pro-inflammatory metabolite products. N-3 PUFA can also be converted into specialized proteolytic mediators (SPMs), such as maresin, resolvin and lipoxin, which can inhibit the synthesis of inflammatory cytokines and limit the entry of leukocytes into damaged tissues.[15]

Singer et al found that in patients with ARDS, administration of an enteral diet enriched with EPA, GLA, and antioxidants for 14 days significantly improved oxygenation and reduced duration of mechanical ventilation. A meta-analysis of Pontes-Arruda et al, found that enteral nutrition fortified with EPA, GLA, and antioxidants in ARDS patients using mechanical ventilation significantly reduced mortality, duration of mechanical ventilation, and duration of Intensive Care Unit (ICU) hospitalization. A double-blind randomized clinical trial tested the effects of N-3 PUFA supplementation in 101 critically ill patients with COVID-19. EPA and DHA supplementation was associated with better survival at 1 month and had positive effects on respiratory and metabolic acidosis (increased arterial pH and bicarbonate concentrations). [15]

Vitamin D has a strong direct effect on B lymphocytes that on the process of inhibiting cytokine-mediated B cell activation by acting on T helper cells. Yao Deng et al (2023) found that Vitamin D was negatively associated with the concentration of anti-wild-type virus antibodies at pre- and post-vaccine day-98 (OR= −0.331) and (OR = −0.317), and with anti-omicron variant antibodies after vaccine day-98 (OR = 0.940). Meanwhile, vitamin A (retinol) and vitamin E (α-tocopherol) have no relationship at all. [16,17]

The effects of vitamin D on immunogenicity are complex, and the relationship between vitamin D and antibody responses to COVID-19 vaccines is inconsistent in current studies. Even a sub-study in a randomized controlled trial CORONAVIT reported that vitamin D supplementation did not affect the protective efficacy or immunogenicity of SARS-CoV-2 mRNA. [16,17]

In this study, PULMOSOL was used, whose composition consists of: plant oil (a mixture of Sunflower oil and Rapeseed oil), medium chain triglycerides, vitamins A, D, E and other compositions. This difference in composition can also affect the outcomes, so that it can explain the reason why this study did not get a significant relationship with PCO2 or patient outcomes.[18]

Several studies have also found a non-significant association between high-fat liquid diets and patient outcomes, either for general ARDS or in COVID-19 patients. The study by Shirai et al found no-association between enteral diet providing that containing EPA, GLA, and antioxidants with reduced need for mechanical ventilation or decreased mortality in critically ill ARDS patients in the ICU. A double-blind randomized study of 58 ARDS patients with N-3 PUFAs found non-significant statistically differences in ICU length of stay. Langlois et al indicated that the effects of N-3 PUFA, GLA, and antioxidants depended on the route and method of providing.[15]

In addition, dysbiosis of the respiratory tract and gastrointestinal tract in COVID-19 patients which could be a factor in adverse outcome of the patients in this study. Based on a meta-analysis of 13 studies, COVID-19 patients showed a decrease in airway microbiota composition, and it was greater in critically ill COVID-19 patients. There was a decrease in *Proteobacteria* and *Fusobacteria* in COVID-19 patients compared to controls. It is known that a decrease in the phyla *Proteobacteria* and *Actinobacteria* in the oropharynx correlates with greater disease severity. Critically ill COVID-19 patients also exhibited reduced *Bifidobacterium* and *Clostridium*, and the presence of *Salmonella, Scardovia*, *Serratia*, *Pectobacteriaceae*, and *Pseudomonas* taxa, which are known to be associated with pathogenic conditions such as severe acute respiratory syndrome. Another characteristic of the airway microbiota in critically ill COVID-19 patients are the lower diversity and more non-fermenting bacteria such as the genera *Acinetobacter*, *Pelomonas*, *Ralstonia*, and *Sphingomonas.* These changes may be due to intubation and mechanical ventilation. In addition, the gut microbiota of COVID-19 patients was found to correlate with cytokines, chemokines, and other inflammatory mediators, suggesting that the gut microbiota may play a role in modulating host immune responses and potentially influencing disease severity and outcome.[19]

Patients with severe COVID-19 often experience ARDS due to an abnormal inflammatory response in lung tissue or a cytokine storm. During the inflammatory response, pulmonary capillaries and alveoli are damaged, increasing their permeability to fluids and proteins, thereby causing fluid accumulation in the lungs. ARDS is manifested by difficulty breathing and hypoxemia. Patients with severe ARDS have an increased risk of sepsis and heart attack, vital organ failure, and death. About 20% of hospitalized COVID-19 patients require ICU. [20]

Inpatients with critical illness have a higher risk of malnutrition, 38.78% of ICU patients are malnourished. Moderate and severe malnutrition based on GLIM criteria and CRP levels >5 mg/dL, more common in the ICU (70%). A cohort study of COVID-19 ICU patients in Morocco, malnutrition diagnose was 14.6% and nutritional risk was 65.9%. [20]

Malnutrition in COVID-19 ICU patients occurs for several reasons, including increased metabolism due to inflammation, decreased food intake, mechanical ventilation, gastrointestinal intolerance, and other nutritional contraindications. Furthermore, malnutrition is associated with poorer clinical outcomes in the ICU including death and increased length of stay, cause the greater systemic inflammation, poorer kidney function, and longer periods of hospitalization. In a retrospective study in China the risk of death in the ICU increased by 20% for each point increase in mNUTRIC score. In addition, the acute phase inflammatory response in severe COVID-19 can cause albumin levels to decrease due to visceral protein homeostasis changes in the form of repriorization of hepatic protein synthesis. Hypoalbuminemia is associated with poor outcome, as it can cause interstitial edema leading to tissue damage, and digestive dysfunction. Liu et al (2020) observed that a 10 g/L difference in baseline albumin concentration was associated with a 5-fold increase in ARDS and a 2-fold increase in mortality.[20]

Most expert guidelines (ESPEN, ASPEN/SCCM, etc.) recommend early feeding (within 24-48 hours of ICU admission) and prioritizing EN (enteral nutrition) than PN (parental nutrition). The expert guidelines for critically ill hospitalized patients recommend a calorie requirement of 15-20 kcal/kg/day and hypocaloric feeding. High protein EN formulas and isosmotic polymers are recommended. The ASPEN/SCCM and ESPEN COVID-19 guidance addresses the potential of fish oil in EN and PN formulations. Fish oil containing *Eicosapentaenoic Acid* (EPA) and *Docosahexaenoic Acid* (DHA) may help ARDS patients with cytokine storm through immunomodulatory effects by increasing oxygenation and reducing ventilation time and hospitalization.[20]

Enteral nutrition through NGT or parenteral nutrition can be used in situations where patients are on a mechanical ventilator. Enteral nutrition is associated with less infection risk than parenteral nutrition and has beneficial effects on intestinal microbial flora, length of hospitalization, and malnutrition. However, enteral nutrition through NGT is associated with side effects such as nosocomial sinusitis and tracheobronchial aspiration of gastric contents, and mask leakage with reduced NIV efficiency.[I] Study by Nicolas Terzi et al. on ICU patients with NIV, found that patients on EN nutrition had a higher incidence of infections (HR 2.2), higher incidence of VAP (Ventilator Associated Pneumonia) (HR 6.9), higher mortality (HR 2.3), and lower ventilator-free days (RR 0.7), when compared to the group that received no nutrition at all on the first 2 days of NIV. [21].

CONCLUSION

The study was conducted on critically ill COVID-19 patients, with more than half of the outcomes dying. Some of the reasons have been identified as the eldery patients and had comorbidities, so when they were sent to the hospital they were in severe condition.

Providing high-fat liquid food in patients with respiratory failure will improve the condition of respiratory failure more significantly than standard composition liquid feeding. In this study, statistically there was non-significance in providing high-fat liquid food in improving respiratory disorder of Covid-19 patients with critical illness. Suggestions for future research is to conduct studies with more samples, especially in patients with severe respiratory disorders, assessed the effect of providing a diet of high-fat liquid foods.

Declaration by Authors:

This research was supported by the *Research Project Covid-19*, PULMOSOL provider by Kalbe FIMA, and M Djamil General Hospital Padang. The authors thank colleagues from the Department of Clinical Nutrition, Departement of Clinical Pharmacology, Departement of Pulmonology and Respiratory for providing insight, assistance and expertise that had greatly helped authors throughout this research.

Ethical Approval: Approved

Acknowledgement: None

Source of Funding: From the *Research Project Covid-19*

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. WHO. Rolling updates on coronavirus disease (COVID-19) [Internet]. 2020 [cited 2020 May 26]. Available from: https://www.who.int/emergencies/diseases/novelcoronavirus-2019/events-as-they-happen
2. Barazzoni R, Bischoff SC, Breda J, Pirlich M, Singer. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-1 infection. Clinical Nutrition;1631-38;39;2020. Available at: http://www.elsevier.com/locate/clnu
3. Barthon, BS, Wood LG. Nutrition and respiratory health- feature review. Nutrients. January 2015
4. Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, et.al. Vitamin D and Covid-19. Eurean Journal of Endocrinology (2020) 183, R133-R147.
5. Hernandez JL, Nan D, Fernandez-Ayala M, et.al. Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. The Journal of clinical Endocrinology & metabolism, (2020), vol. XX. 1-11
6. Allen K, Hoffman L. Enteral nutrition in the mechanically ventilated patient. Aspen. 2019.
7. Faramawy, Allah, Batrawy, Amer. Impact of high fat low carbohydrate enteral feeding on weaning from mechanical ventilation. Elsevier. The Egyptian society of cest disease and tuberculosis production and hosting by Elsevier. July 2014.
8. Rainer L, Bachner F, Eglau K, Ostermann H, Siebert U, Zuba M. Comorbidities and COVID-19 hospitalization, ICU admission and hospital mortality in Austria: A retrospective cohort study. Wien Klin Wochenschr. 2022 Dec;134(23-24):856-867.
9. Kautzky-Willer A. Does diabetes mellitus mitigate the gender gap in COVID-19 mortality? Eur J Endocrinol. 2021;185(5): C13–C7
10. Beltrão FEL, Beltrão DCA, Carvalhal G, Beltrão FNL, de Aquino IM, Brito TDS, Paulino BC, Aires E, Viegas D, Hecht F, Halpern B, Pordeus LCM, Gonçalves MDCR, Ramos HE. Low muscle mass and high visceral fat mass predict mortality in patients hospitalized with moderate-to-severe COVID-19: a prospective study. Endocr Connect. 2022 Sep 26;11(10): e220290.
11. Tadayon Najafabadi B, Rayner DG, Shokraee K, Shokraie K, Panahi P, Rastgou P, et al. Obesity as an independent risk factor for COVID-19 severity and mortality. Cochrane Database of Systematic Reviews 2023, Issue 5. Art. No.: CD015201. DOI: 10.1002/14651858.CD015201. Accessed 05 August 2023.
12. Favre G, Legueult K, Pradier C, Raffaelli C, Ichai C, Iannelli A, Redheuil A, Lucidarme O, Esnault V. Visceral fat is associated to the severity of COVID-19. Metabolism. 2021 Feb; 115:154440
13. Ceriello A, Standl E, Catrinoiu D, Itzhak B, Lalic NM, Rahelic D, Schnell O, Škrha J, Valensi P; "Diabetes and Cardiovascular Disease (D&CVD)" Study Group of the European Association for the Study of Diabetes (EASD). Issues for the management of people with diabetes and COVID-19 in ICU. Cardiovasc Diabetol. 2020 Jul 20;19(1):114.
14. Nourmohammadi M, Moradi Moghdam O, Niakan Lahiji M, Vahdat Shariatpanahi Z. High-fat low-carbohydrate enteral feeding enriched with olive oil and acute respiratory failure: A double-blind, randomized, controlled trial. Clin Nutr ESPEN. 2022 Dec; 52:144-150.

15. Lampova B, Doskocil I, Kourimska L, Kopec A. N-3 polyunsaturated fatty acids may affect the course of COVID-19. Front Immunol. 2022 Sep 27; 13:957518.
16. Deng Y, Huang L, Liu P, Geng X, Lin Z, Zheng Z, Zhan M, Zhang Z, Liu J, Sun T. Association of fat-soluble vitamins (A, D, and E) status with humoral immune response to COVID-19 inactivated vaccination. Front Nutr. 2023 May 16; 10:1167920
17. Jolliffe DA, Vivaldi G, Chambers ES, Cai W, Li W, Faustini SE, et al. Vitamin D supplementation does not influence SARS-CoV-2 vaccine efficacy or immunogenicity: sub-studies nested within the CORONAVIT randomised controlled trial. Nutrients. (2022) 14:18. doi: 10.3390/nu14183821
18. KalbeMed.PULMOSOL.https://www.uniqu epharmacy.lk/product/PULMOSOL-vanilla-150g/. Diakses Agustus 2023.
19. Ancona G, Alagna L, Alteri C, Palomba E, Tonizzo A, Pastena A, Muscatello A, Gori A, Bandera A. Gut and airway microbiota dysbiosis and their role in COVID-19 and long-COVID. Front Immunol. 2023 Mar 8; 14:1080043.
20. Thomas S, Alexander C, Cassady BA. Nutrition risk prevalence and nutrition care recommendations for hospitalized and critically-ill patients with COVID-19. Clin Nutr ESPEN. 2021 Aug; 44:38-49.
21. Terzi N, Darmon M, Reignier J, Ruckly S, Garrouste-Orgeas M, Lautrette A, Azoulay E, Mourvillier B, Argaud L, Papazian L, Gainnier M, Goldgran-Toledano D, Jamali S, Dumenil AS, Schwebel C, Timsit JF; OUTCOMEREA study group. Initial nutritional management during noninvasive ventilation and outcomes: a retrospective cohort study. Crit Care. 2017 Nov 29;21(1):293

How to cite this article: Dewi Susanti Febri, Gestina Aliska, Afriani Afriani, Nisnawati, Azzah Saniyyah. The effect of high fat formula liquid feeding on the value of PCO_2, and duration of use of respiratory aids for COVID-19 patients with critical illness. *International Journal of Research and Review*. 2023; 10(10): 279-290. DOI: *https://doi.org/10.52403/ijrr.20231035*

******