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Early Parenteral Nutrition (PN) As A Mortality Risk Factor in COVID-19 Patients at the Intensive Care Unit (ICU) of RSUP Dr. Kariadi

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Abstract

Mortality among COVID-19 patients admitted to intensive care units (ICUs) is consistently reported to be higher than among non-ICU patients. Early parenteral nutrition (PN) is generally avoided due to its potential complications; however, many critically ill COVID-19 patients require PN because of inadequate enteral intake or contraindications to enteral nutrition. This study aimed to evaluate the effect of early PN administration and other clinical risk factors on mortality among COVID-19 patients treated in the ICU of Dr. Kariadi General Hospital. This analytical observational study used a retrospective cohort design based on secondary data from COVID-19 patients admitted to the ICU of Dr. Kariadi General Hospital between March and September 2020. A total sampling approach was applied, including all patients aged ≥18 years who received PN, EN, or a combination of both during ICU care. Statistical analyses were conducted using Chi-square tests and logistic regression. A total of 188 patients were included, with a mean age of 53.5 ± 13.0 years; 62.8% were male and 66.5% had comorbidities. ARDS was present in 89.3% of patients, and 56.4% required mechanical ventilation. Early PN was administered to 32.8% of patients. By day 3 of ICU care, mean energy and protein adequacy reached 32.4% and 66.6%, respectively. Overall ICU mortality was 53.7%. Bivariate analysis showed significant associations between mortality and comorbidities ($p = 0.023$), mechanical ventilation ($p < 0.0001$), energy deficit ($p = 0.002$), and protein deficit ($p = 0.039$). Early PN was not significantly associated with mortality ($p = 0.918$). Multivariate logistic regression identified mechanical ventilation (adjusted for ARDS status; RR 6.20, 95% CI 1.29–29.72; $p = 0.022$) and energy deficit (RR 2.15, 95% CI 1.01–4.57; $p = 0.045$) as independent predictors of mortality. Early PN was not associated with increased mortality among critically ill COVID-19 patients in this ICU cohort. In contrast, mechanical ventilation—particularly in patients with ARDS—and inadequate energy intake were independent predictors of mortality. These findings highlight the importance of optimizing energy delivery and implementing careful ventilatory management to improve clinical outcomes in critically ill COVID-19 patients.

Keywords: Risk factors, early PN, mortality, COVID-19, ICU, mechanical ventilation, energy deficit

INTRODUCTION

Although global attention to COVID-19 has diminished since the international public health emergency was lifted, the disease continues to provide important insights for critical care practice, particularly in relation to nutritional management and organ support in severe respiratory illness. During the early phase of the pandemic in 2020, critically ill COVID-19 patients presented unique challenges for ICU teams, including profound systemic inflammation, respiratory failure requiring mechanical ventilation, and marked hypermetabolism that frequently resulted in significant nutritional deficits. These conditions often made it difficult to meet energy and protein requirements through enteral nutrition alone, thereby necessitating the use of parenteral nutrition (PN).(1-3) Although the incidence of COVID-19 has since declined, knowledge gained from ICU management remains relevant for other severe viral pneumonias and for preparedness in future respiratory pandemics. Understanding how factors such as the timing of PN initiation, ventilation strategies, and adequacy of energy intake influence patient outcomes is essential to refining critical care nutrition protocols.

COVID-19, caused by SARS-CoV-2, was declared a pandemic by the World

Health Organization (WHO) in March 2020. Despite global declines in cases and deaths by May 2021, Indonesia, particularly the province of Central Java, continued to experience substantial disease burden. Approximately 5% of COVID-19 patients develop critical illness, with ICU mortality rates reported between 45–60%, especially among those requiring mechanical ventilation.(4) Mortality risk factors include advanced age, organ dysfunction, and poor nutritional status. Nutritional support is therefore integral to patient management. Critically ill COVID-19 patients commonly exhibit hypermetabolism and rapid muscle loss, while being unable to eat orally, thus requiring enteral nutrition (EN) or, when necessary, PN.(4-6)

Risk factors for mortality include advanced age, organ dysfunction, and nutritional status. Nutritional support plays a crucial role in patient outcomes. Critically ill COVID-19 patients often experience hypermetabolism and muscle mass loss, yet are frequently unable to eat orally, thus requiring enteral nutrition (EN) or parenteral nutrition (PN).(5,7,8)

The optimal timing for PN initiation in critically ill patients remains a subject of ongoing debate due to varied findings across studies. Some evidence suggests that early PN (<48 hours) may increase the risks of infection, hyperglycemia, and delayed recovery, potentially through mechanisms such as autophagy suppression, particularly in patients who are well-nourished or at low risk of malnutrition.(9-13) ESPEN guidelines recommend initiating PN within 3–7 days if EN is contraindicated, with early PN considered only in cases of severe malnutrition or high nutritional risk, such as among patients with sepsis or shock for whom EN is not feasible.(14,15) Large trials, including EPaNIC and CALORIES, have shown that delaying PN can reduce infection rates without increasing mortality,(9,16) whereas in severely malnourished patients, PN may reduce the risk of death and other complications.(17,18) Thus, decisions regarding PN administration should be individualized based on nutritional status, clinical condition, infection risk, and an assessment of the balance between potential benefits and cost-related risks.(5,15,19)

This study aims to evaluate whether early PN administration constitutes a risk factor for mortality among critically ill COVID-19 patients in the ICU of Dr. Kariadi General Hospital.

METHOD

Study Design and Setting

This analytical observational study employed a retrospective cohort design and was conducted in the Intensive Care Unit (ICU) of Dr. Kariadi General Hospital, Semarang, Indonesia. The study analyzed secondary data extracted from the electronic medical records (EMR) of patients admitted between March and September 2020.

Population and Sampling

The study population comprised adult patients (≥18 years) with a confirmed diagnosis of COVID-19 who received nutritional therapy during their ICU stay. A total sampling approach was used, whereby all eligible patients who met the inclusion criteria within the study period were included.

Inclusion Criteria

- Confirmed diagnosis of COVID-19 based on RT-PCR results
- Age ≥18 years
- Receipt of enteral nutrition (EN), parenteral nutrition (PN), or a combination of both during ICU hospitalization

Exclusion Criteria

- Presence of underlying conditions known to independently influence mortality or nutritional metabolism (e.g., malignancy, chronic kidney disease requiring dialysis, advanced liver failure, or uncontrolled endocrine disorders)
- Transfer to or from another healthcare facility before completion of ICU treatment
- Missing or incomplete key clinical or nutritional data in the EMR (e.g., absence of documented nutritional intake or mortality outcome)

Definition of Variables

Early parenteral nutrition (PN) was defined as initiation of PN within ≤3 days (≤72 hours) after ICU admission, whereas late PN referred to initiation >3 days after admission. Energy deficit was defined as failure to achieve ≥80% of the prescribed energy requirement by day 3 of ICU care. Protein deficit was defined as failure to achieve ≥80% of the prescribed protein requirement by day 3. Mechanical ventilation (MV) refers to the use of invasive ventilatory support during ICU treatment. Mortality was defined as in-hospital death occurring during ICU admission.

Data Collection and Analysis

Data extracted from EMR records included demographic characteristics, comorbidities, type and timing of nutritional therapy, ARDS status, use of mechanical ventilation, and clinical outcomes. Statistical analyses were performed using SPSS software.

Descriptive statistics were presented as means ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. Associations between categorical variables were evaluated using the Chi-square test. Variables with $p < 0.25$ in bivariate analysis, as well as those deemed clinically relevant, were entered into a multivariate logistic regression model to identify independent predictors of mortality. Results were expressed as risk ratios (RR) with 95% confidence intervals (CI), and statistical significance was determined at $p < 0.05$.

The study protocol was approved by the Medical Research Ethics Committee of Diponegoro University and Dr. Kariadi General Hospital, and all procedures adhered to the ethical principles outlined in the Declaration of Helsinki.

RESULT

A total of 188 COVID-19 patients admitted to the ICU were included in the analysis. The mean age was 53.5 ± 13.0 years, with 62.8% being male and 66.5% presenting with at least one comorbidity, most commonly diabetes mellitus and hypertension. The majority of patients developed ARDS (89.3%), and 56.4% required mechanical ventilation (MV). Early PN was initiated in 32.8% of patients, while most received enteral nutrition (EN) alone or in combination with supplemental PN. By the third day of ICU care, mean energy adequacy was 32.4%, and mean protein adequacy reached 66.6%. The overall ICU mortality rate was 53.7%.

These findings are consistent with international reports demonstrating that male sex and obesity contribute to higher COVID-19 mortality risk, and that comorbidities further exacerbate disease severity through mechanisms involving systemic inflammation, immunosenescence, and impaired organ function.(20-22)

Table 1. Sample Characteristics

	n (%)	Mean ± SD (n = 188)	Min - Max
Age		53.5 ± 13.0	25 - 85
Age Group			
Elderly	62 (33.0)		
Adult	126 (67.0)		
Sex			
Men	118 (62.8)		
Women	70 (37.2)		
BMI		26,2 ± 4.7	12.8 - 48
Asia Pacific Classification			
Morbid Obesity	8 (4.3)		
Grade II Obesity	24 (12.8)		
Grade I Obesity	84 (44.7)		
Overweight	31 (16.5)		
Normal weight	37 (19.7)		
Underweight	4 (2.1)		

Comorbidity **Yes** **No**	 125 (66.5) 63 (33.5)		
Type of Comorbidity **Cardio-cerebrovascular disease** **Diabetes Mellitus** **Hypertension**	 37 (19.7) 66 (35.1) 63 (33.5)		
ARDS Status **Yes** **No**	 167 (89.3) 20 (10.7)		
ARDS Severity **Severe** **Moderate** **Mild**	 71 (42.5) 66 (39.5) 30 (18.0)		
MV Usage **Yes** **No**	 106 (56.4) 82 (43.6)		
Feeding Route **EN + supplemental PN** **EN**	 124 (66.0) 62 (33.0)		
PN Starting Day		3,9 ± 2.4	1 - 15
Early PN **Yes** **No**	 39 (32.8) 80 (67.2)		
Energy and Protein Target Achievement (Day 3) **EN + sPN** **EN**	 61 (32.4) 124 (66.0)		
Mortality **Death** **Survive**	 101 (53.7) 87 (46.3)		
Energy Deficit **Yes** **No**	 54 (28.7) 134 (71.3)		
Protein Deficit **Yes** **No**	 81 (43.1) 107 (56.9)		

Barbosa et al. reported that by day 4 of ICU care, 75.6% of COVID-19 patients received enteral nutrition (EN), 8.7% received total parenteral nutrition (TPN), and 13% received a combination of both.(23) In comparison, the present study demonstrated a lower achievement of nutritional adequacy, consistent with previous reports documenting persistent deficits among critically ill COVID-19 patients. Silvah et al. noted protein deficits of up to 75%, whereas Melika et al.(24,25) found that by day 5 of ICU admission, energy and protein intake reached only 46% and 58% in survivors, and 42% and 50% in non-survivors, respectively.

The ICU mortality rate in this study was 53.7%, which is similar to mortality reported in China (61.5%) and Indonesia (44.67%).(4,26) Multivariate analysis further examined factors contributing to mortality. As presented in **Table 2**, mechanical ventilation (MV) was strongly associated with increased mortality, conferring a 43.68 -fold higher risk. **Table 3** shows no significant association between early parenteral nutrition (PN) and mortality. In contrast, both energy and protein deficits were significantly associated with adverse outcomes. Patients with an energy deficit had a 3.09-fold increased mortality risk (**Table 4**), while those with a protein deficit had a 1.93-fold increased risk (**Table 5**).

Table 2. Association Between Mechanical Ventilation Use and Mortality

		Mortality	
		Non-survivor	Survivor
VM Usage	Yes	91 (90.1)	15 (17.2)
	No	10 (9.9)	72 (82.8)
	Total	101 (100)	81 (100)

x^2 100.886; df 1; p: <0.0001 RR 43.68 (95% CI 18.52 – 102.99)

Table 3. Association Between Early Parenteral Nutrition and Mortality

		Mortality	
		Non-survivor n (%)	Survivor n (%)
Early PN	Yes	31 (50.0)	30 (52.6)
	No	31 (50.0)	27 (47.4)
	Total	62 (100)	57 (100)

x^2: 0.82; df: 1; p:0.918 RR 0.90 (95% CI 0.43-1.84)

Table 4. Association Between Energy Deficit and Mortality

		Mortality	
		Non-survivor n (%)	Survivor n (%)
Energy Deficit	Yes	39 (38.6)	15 (17.2)
	No	62 (61.4)	72 (82.7)
	Total	101 (100)	87 (100)

x^2: 10.42; df: 1; p: 0.002 RR 3.09 (95% CI 1.52-5.99)

Table 5. Association Between Protein Deficit and Mortality

		Mortality	
		Non-survivor n (%)	Survivor n (%)
Protein Deficit	Yes	51 (50.5)	30 (82.7)
	No	50 (49.5)	57 (34.4)
	Total	101 (100)	87 (100)

x^2: 4.88; df: 1; p: 0.039 RR 1.93 (95% CI 1.07-3.49)

Table 6. Results of Multivariate Analysis

Variable	B	Wald	P value	RR (CI 95%)
Comorbidity	0.550	2.654	0.103	1.73 (0.89 – 3.36)
ARDS Status x VM Usage	**1.826**	**5.218**	**0.022**	**6.20 (1.29 – 29.72)**
Energy Deficit	**0.770**	**4.034**	**0.045**	**2.15 (1.01 – 4.57)**
Protein Deficit	0.226	0.462	0.497	0.25 (0.65 – 2.40)

These findings underscore the importance of sufficient nutritional support in critically ill COVID-19 patients. Although the timing of PN initiation did not independently influence mortality, inadequate achievement of energy and protein requirements markedly increased the risk of death, highlighting the need for individualized nutrition plans, ongoing monitoring, and prompt adjustment of nutritional therapy to optimize clinical outcomes.

DISCUSSION

Mechanical Ventilation and Mortality

Mortality in this cohort occurred predominantly among patients requiring mechanical ventilation (MV), consistent with previous studies reporting mortality rates exceeding 50% among ventilated COVID-19 patients.(20,22,27,28) MV likely reflects the severity of ARDS and contributes to mortality through ventilator-associated complications and reduced ability to deliver adequate nutrition.[29] These findings reinforce the importance of strategies aimed at preventing ventilator-induced lung injury, including minimizing alveolar overdistention, avoiding excessive oxygen exposure, and preventing cyclical alveolar collapse.

Timing of Parenteral Nutrition

Meta-analyses have demonstrated no significant difference in mortality between early enteral nutrition (EN) and early parenteral nutrition (PN) in critically ill patients.(26,30,31) Similarly, in this study, the proportion of patients receiving early PN was comparable to those receiving later PN, and mortality did not differ significantly between groups ($p = 0.918$). These results align with previous studies (10, 32, 33) indicating that early PN does not influence ICU mortality, although it may facilitate achievement of energy and protein goals.(12,17) Other trials comparing early versus delayed PN initiation(31, 34) likewise found no significant difference in mortality.

Energy and Protein Deficits

Although fewer patients experienced energy and protein deficits than those who did not, chi-square analysis revealed significant associations between these deficits and mortality. This observation is consistent with findings from Silva et al.,(25) who emphasized that critically ill COVID-19 patients are highly vulnerable to malnutrition and exhibit higher mortality when energy–protein intake is inadequate. A prospective cohort study (35) similarly demonstrated increased mortality among patients with energy and protein deficits. Additionally, Silvah et al. reported lower mortality among ICU patients receiving >0.8 g/kg/day of protein. Gastrointestinal intolerance and hemodynamic instability likely contributed to nutritional deficits in ICU patients.(36)

Several studies and systematic reviews recommend early PN, whether supplemental or total, as a strategy to meet energy and protein targets in critically ill COVID-19 patients.(37,24,38) Early PN may also reduce the risk of intestinal ischemia and decrease healthcare worker exposure to aerosolized droplets by reducing the need for enteral tube manipulation.(21)

Multivariate Analysis

Bivariate analyses identified significant associations between mortality and comorbidities, MV use, energy deficit, and protein deficit, while age, ARDS status, and early PN showed no significant associations. Variables with $p < 0.25$ or with strong theoretical relevance, comorbidities, MV use, early PN, energy deficit, and protein deficit, were included in the multivariate model.

After adjustment, two factors remained independently associated with mortality. MV use increased the risk of death by 6.2-fold, regardless of ARDS status. Energy deficit was also a strong predictor, conferring a 2.15-fold increased risk of mortality. MV use may directly compromise energy and protein adequacy by limiting feeding routes and contributing to hemodynamic instability. (24,39) The notable interaction between MV and ARDS reinforces that patients with severe ARDS require early MV and are at elevated risk for complications without effective, tailored management.(29, 40)

Clinical Implications

Energy requirements in critically ill COVID-19 patients are higher than in non-critically ill patients due to hypercatabolic states.(41, 42) Many severe cases fail to meet these elevated requirements, and adequate nutritional intake in the acute phase has been associated with improved survival.(35) Conversely, delayed nutritional therapy contributes to worsening comorbidities, respiratory decline, cytokine storm progression, and ultimately increased mortality.(43, 44) These findings underscore the critical importance of timely, adequate nutritional support in critically ill COVID-19 patients, particularly those receiving mechanical ventilation.

Limitations

This study has several limitations. First, energy requirements were not measured using indirect calorimetry, the gold standard recommended by international guidelines, which may have affected the accuracy of energy target estimations. Second, PN administration was not stratified into supplemental versus total PN, limiting detailed subgroup analysis. Lastly, micronutrient levels were not evaluated despite their potential relevance to outcomes in critically ill COVID-19 patients.

CONCLUSION

Early administration of parenteral nutrition (PN) was not identified as a risk factor for mortality among COVID-19 patients admitted to the ICU of Dr. Kariadi General Hospital. In contrast, comorbidities, the use of mechanical ventilation (MV), and deficits in both energy and protein intake were significantly associated with increased mortality. Multivariate analysis further demonstrated that MV, adjusted for ARDS status, and energy deficit remained independent predictors of death among critically ill COVID-19 patients.

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