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ENERGY DEFICIT AND MORTALITY IN CRITICALLY ILL COVID-19 PATIENTS: EXPLORING THE MODIFYING ROLE OF ARDS

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ABSTRAK

Pasien COVID-19 kritis sering mengalami kondisi hipermetabolik dan katabolik yang meningkatkan kebutuhan energi dan protein, sehingga berisiko mengalami defisit nutrisi yang dapat memperburuk luaran klinis. Penelitian ini bertujuan menilai hubungan defisit energi dan protein kumulatif dengan mortalitas di unit perawatan intensif (ICU) serta mengeksplorasi peran acute respiratory distress syndrome (ARDS) sebagai faktor pemoderasi. Studi kohort retrospektif ini melibatkan 188 pasien dewasa dengan COVID-19 yang dirawat di ICU minimal tujuh hari. Kebutuhan energi dan protein ditentukan berdasarkan pedoman nutrisi ICU, sedangkan asupan aktual dihitung dari kombinasi catatan nutrisi enteral dan parenteral selama tujuh hari pertama perawatan. Defisit nutrisi didefinisikan sebagai asupan <80% dari target yang diresepkan, dan dianalisis menggunakan regresi logistik multivariat dengan penyesuaian terhadap usia serta komorbiditas, termasuk interaksi dengan ARDS. Defisit energi awal berhubungan secara independen dengan peningkatan risiko kematian di rumah sakit, sedangkan defisit protein menunjukkan arah efek yang konsisten namun tidak mencapai signifikansi statistik. Interaksi antara ARDS dan defisit energi atau protein tidak bermakna, tetapi estimasi efek menunjukkan kecenderungan dampak yang lebih besar pada pasien dengan gangguan respirasi berat dan kebutuhan ventilasi mekanik. Temuan ini menegaskan bahwa pencegahan defisit energi pada fase awal perawatan ICU merupakan komponen kunci tata laksana nutrisi yang berpotensi memperbaiki luaran pada pasien COVID-19 kritis.
Kata kunci: *COVID-19, Defisit Energi, Mortalitas, ICU, ARDS*

ABSTRACT

Critically ill patients with COVID-19 frequently develop a hypermetabolic and catabolic state that increases energy and protein requirements, placing them at risk of cumulative nutritional deficits and poor clinical outcomes. This study aimed to evaluate the association between cumulative energy and protein deficits and intensive care unit (ICU) mortality and to explore whether acute respiratory distress syndrome (ARDS) modifies these relationships. A retrospective cohort study was conducted in 188 adult COVID-19 patients who stayed in the ICU for at least seven days. Energy and protein requirements were determined according to ICU nutrition guidelines, while actual intake from enteral and parenteral nutrition was recorded over the first seven ICU days. Nutritional deficits were defined as intake <80% of the prescribed target and analyzed using multivariable logistic regression adjusted for age and comorbidities, with additional interaction terms for ARDS. Early energy deficit was independently associated with higher in-hospital mortality, whereas protein deficit showed a similar direction of effect but did not reach statistical significance. Interactions between ARDS and either energy or protein deficits were not statistically significant, although effect estimates suggested a tendency

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toward greater harm in patients with severe respiratory failure and mechanical ventilation. These findings indicate that preventing early energy deficit is a key component of ICU nutrition therapy and may help improve outcomes in critically ill patients with COVID-19.
Keywords: *COVID-19, Energy Deficit, Mortality, ARDS, ICU.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is associated with substantial morbidity and mortality, particularly among critically ill patients requiring intensive care support and invasive mechanical ventilation (Yang et al., 2024; Auld et al., 2023). In severe cases, COVID-19 leads to respiratory failure, systemic inflammation, multi-organ dysfunction, and prolonged ICU stay, which together complicate clinical and nutritional management (Thibault et al., 2023; Arkin et al., 2022). These complex physiological alterations increase patients' vulnerability to malnutrition and poor outcomes, making comprehensive supportive care, including optimal nutrition therapy, essential in the ICU setting (Barazzoni et al., 2020).

Critically ill COVID-19 patients frequently exhibit a hypermetabolic and catabolic state with increased resting energy expenditure and accelerated protein breakdown, which can result in substantial cumulative energy and protein deficits when nutritional targets are not achieved early (Whittle et al., 2025; Niederer et al., 2024). This condition is often aggravated by mechanical ventilation, deep sedation, systemic inflammation, and immobilization, and has been associated with rapid loss of skeletal muscle mass, impaired immune responses, delayed recovery, and prolonged ventilator dependence (Yu et al., 2021; de Waele et al., 2021). Observational studies have shown that inadequate energy and protein intake is related to higher mortality and worse functional outcomes in critically ill COVID-19 patients, whereas achieving higher nutritional adequacy is linked to improved prognosis (Compher et al., 2023; Silvah et al., 2024; de Vries et al., 2021).

Adequate nutrition is a cornerstone of supportive care in critical illness because it helps maintain metabolic stability, preserve lean body mass, and support long-term functional recovery (Singer & Thibault, 2026; Thibault et al., 2023). However, evidence regarding the optimal amount and timing of energy and protein delivery in critically ill COVID-19 patients remains inconsistent. Some investigations have demonstrated that reaching individualized energy and protein targets is associated with lower mortality, particularly in mechanically ventilated patients (Hajimohammadebrahim-Ketabforoush et al., 2023; Heyland et al., 2025; van Zanten et al., 2023), whereas other data suggest that overly aggressive early feeding may not confer additional benefit and could worsen metabolic stress in selected populations (Arkin et al., 2022; Rhodes et al., 2024). These inconsistencies highlight the need for individualized nutritional strategies based on patients' clinical conditions and disease severity.

Acute respiratory distress syndrome (ARDS), one of the most severe complications of COVID-19, may further modify metabolic responses and nutritional requirements in critically ill patients. ARDS is characterized by severe hypoxemia, diffuse pulmonary inflammation, impaired gas exchange, and increased ventilatory workload, all of which contribute to elevated metabolic demands and negative energy balance (Martindale et al., 2025; Ochoa et al., 2023). Patients with ARDS frequently require prolonged mechanical ventilation and deep sedation, which may interfere with enteral nutrition delivery and reduce achievement of prescribed nutritional targets. This pathophysiological complexity suggests that the relationship between cumulative nutritional deficits and mortality may differ according to the presence and severity

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of ARDS, although this interaction remains insufficiently explored in current literature (Zhao et al., 2025; Li et al., 2024).

Despite current guidelines emphasizing early, individualized, and adequate nutritional therapy for critically ill COVID-19 patients (Barazzoni et al., 2020; Singer & Thibault, 2026; Martindale et al., 2025), few studies have specifically examined whether ARDS modifies the association between cumulative energy–protein deficits and ICU mortality. Most prior work has focused on overall nutritional adequacy or global outcomes without explicitly considering respiratory severity or ARDS status (Compher et al., 2023; Thibault et al., 2023; van Zanten et al., 2023). Understanding this relationship is important because patients with ARDS may have substantially different metabolic demands and responses to nutritional interventions compared with non-ARDS patients. Therefore, this study aimed to assess the association between cumulative energy and protein deficits and ICU mortality in critically ill COVID-19 patients and to explore whether the presence of ARDS modifies these relationships.

RESEARCH METHODS

This retrospective cohort study was conducted in the intensive care unit (ICU) of a tertiary referral hospital and included adult patients (≥18 years) with laboratory-confirmed COVID-19 admitted between March and September 2020. Patients were selected using consecutive sampling. Eligible patients were those who remained in the ICU for at least seven days and had complete nutritional and outcome records; patients transferred out before day 7 or with missing outcome data were excluded, resulting in a final sample of 188 patients. Demographic and clinical data, including age, sex, body mass index (BMI), comorbidities (hypertension, diabetes, chronic kidney disease, cardiovascular disease), presence of ARDS, use of mechanical ventilation, and clinical outcomes, were extracted from electronic medical records using a standardized data-collection form. Daily nutritional intake data were obtained from routine bedside assessments, combining enteral and parenteral nutrition charts, infusion records, and clinical nutrition physician notes. To enhance data accuracy, intake records were cross-checked by ICU nurses and clinical nutrition physician against medical and pharmacy orders, and any inconsistencies were resolved by consensus before entry into the study database. All data were anonymized in accordance with institutional procedures, and the study protocol received ethical approval (No. 1096/EC/KEPK-RSDK/2022).

Energy and protein requirements were determined according to institutional ICU nutrition guidelines adapted from international recommendations, using 25–30 kcal/kg/day and 1.2–2.0 g protein/kg/day, and were adjusted according to the patient's clinical condition. Cumulative energy and protein intake were calculated over the first seven ICU days. Energy and protein deficits were defined as the percentage difference between prescribed targets and actual intake and were categorized as deficit when intake was <80% of the target and no deficit when intake was ≥80%. The primary outcome was all-cause in-hospital mortality, whereas ICU length of stay and duration of mechanical ventilation were described descriptively. Multivariable logistic regression analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY) to assess the associations between energy and protein deficits and mortality, with separate models for each nutritional variable and interaction terms between ARDS and (1) energy deficit and (2) protein deficit. All models were adjusted for age and comorbidities, statistical significance was set at $p < 0.05$, and model fit was assessed using the Hosmer–Lemeshow goodness-of-fit test.

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RESULTS AND DISCUSSION

Result

This study included a cohort of critically ill COVID-19 patients treated in a tertiary ICU, most of whom presented with multiple risk factors for adverse outcomes. The overall profile reflected a relatively high burden of comorbidities and respiratory failure, consistent with the population typically requiring intensive care support during the pandemic. In addition to severe respiratory compromise, many patients also exhibited nutritional risk characteristics, such as higher body mass index and prolonged ICU stay, which may predispose them to underfeeding. Taken together, these features indicate that the study population was representative of a severely ill group in whom early nutritional adequacy could play an important prognostic role.

Table 1. Baseline Characteristics of Study Population (n = 188)

Variable		n (%) / Mean ± SD
Age (years)		53.5 ± 13.0
	≥60 years	62 (33.0%)
	<60 years	126 (67.0%)
Gender	Male	118 (62.8%)
	Female	70 (37.2%)
Body Mass Index (kg/m²)		26.2 ± 4.7
Comorbidities Status	Comorbidities	125 (66.5%)
	No comorbidities	63 (33.5%)
ARDS Status	ARDS	167 (89.3%)
	No ARDS	20 (10.7%)
Mechanical Ventilation Status	Mechanical ventilation	106 (56.4%)
	No mechanical ventilation	82 (43.6%)
Energy Deficit Status	Energy deficit	54 (28.7%)
	No energy deficit	134 (71.3%)
Protein Deficit Status	Protein deficit	81 (43.1%)
	No protein deficit	107 (56.9%)
	Mortality	101 (53.7%)

Baseline Characteristics

The baseline characteristics underscore that a large proportion of patients had conditions that can amplify the impact of nutritional deficits, including chronic diseases and advanced respiratory support. The frequent occurrence of early energy and protein deficits suggests that achieving prescribed nutritional targets is challenging in this setting, likely due to clinical instability and interruptions in feeding. This context highlights the importance of examining how deviations from nutritional prescriptions may influence survival in such a vulnerable

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population. On this basis, subsequent analyses focused on quantifying the association between early nutritional deficits and mortality and on exploring whether markers of disease severity modified these relationships.

To assess the prognostic role of early energy intake, a multivariable logistic regression model was constructed with mortality as the dependent variable and energy deficit as the main exposure. The model incorporated key clinical covariates, such as age and comorbidity status, to account for baseline differences that might confound the relationship between nutrition and outcome. ARDS status was included both as an independent variable and as an interaction term with energy deficit in order to evaluate potential effect modification by respiratory severity. This modeling strategy allowed us to distinguish the specific contribution of early energy deficit from that of general illness severity and pre-existing risk factors.

Table 2. Multivariable Logistic Regression Analysis of Energy Deficit and Mortality

Variable	OR (95% CI)	p-value
Energy deficit	**2.17 (1.03 – 4.58)**	**0.041**
ARDS	0.49 (0.05 – 4.62)	0.533
Energy deficit × ARDS	7.62 (0.56 – 104.3)	0.128
Age	0.99 (0.97 – 1.01)	0.426
Comorbidities	1.58 (0.81 – 3.10)	0.180

The analysis showed that patients who did not achieve their prescribed early energy targets had a substantially higher likelihood of death in the ICU, even after adjusting for age and comorbid conditions. This finding suggests that underfeeding during the initial phase of critical illness may exert an independent adverse effect beyond traditional risk factors. Although ARDS status alone did not emerge as a statistically significant predictor in this model, the interaction term indicated a tendency toward greater harm from energy deficit in patients with more severe respiratory compromise. Overall, these results support the interpretation that early energy adequacy is a clinically important and potentially modifiable determinant of outcome in critically ill COVID-19 patients.

A second multivariable model was developed to examine the relationship between early protein intake and mortality using a similar analytic approach. In this model, protein deficit served as the primary exposure, with age, comorbidities, and ARDS status included as covariates to control for baseline differences in clinical risk. An interaction term between protein deficit and ARDS was added to explore whether respiratory severity might alter the effect of insufficient protein provision. By comparing this model with the energy deficit model, it was possible to evaluate whether energy and protein exert similar or distinct influences on patient outcomes in this cohort.

Table 3. Multivariable Logistic Regression Analysis of Protein Deficit and Mortality

Variable	OR (95% CI)	p-value
Protein deficit	1.43 (0.76 – 2.70)	0.272
ARDS	0.62 (0.11 – 3.50)	0.591

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Variable	OR (95% CI)	p-value
Protein deficit × ARDS	6.00 (0.65 – 54.7)	0.113
Age	0.99 (0.97 – 1.01)	0.437
Comorbidities	1.85 (0.97 – 3.55)	0.064

Association Between Protein Deficit and Mortality

In contrast to the findings for energy deficit, the model for protein deficit did not demonstrate a statistically robust association with mortality, although the direction of the effect was compatible with a modest increase in risk. This pattern suggests that, within the limitations of the sample size, the impact of underfeeding in this population may be driven more strongly by energy shortfalls than by protein alone. The absence of a clear interaction between protein deficit and ARDS further indicates that any additional effect of protein inadequacy may be more subtle and harder to detect in smaller cohorts. Nevertheless, the point estimates remain clinically relevant and justify continued attention to adequate protein delivery as part of comprehensive nutritional management.

Because mechanical ventilation is a marker of both disease severity and practical challenges in delivering nutrition, a stratified analysis was performed to explore whether the association between energy deficit and mortality differed according to ventilatory status. Separate effect estimates were calculated for patients who required invasive mechanical ventilation and for those who did not, using the same definition of early energy deficit. This approach allowed for a more nuanced assessment of whether the prognostic impact of energy intake is amplified in patients with greater respiratory support needs. The results of this stratified analysis are summarized in Table 4.

Table 4. Stratified Analysis of Energy Deficit and Mortality by Mechanical Ventilation Status

Group	OR	95% CI	p-value
Mechanical ventilation (+)	2.74	0.72 – 10.39	0.138
Mechanical ventilation (–)	1.25	0.24 – 6.63	0.793

Stratified Analysis by Mechanical Ventilation Status

The stratified results suggested that the adverse association between early energy deficit and mortality was more pronounced among patients receiving mechanical ventilation, although statistical significance was not achieved due to wide confidence intervals. This trend is consistent with the hypothesis that patients with the highest respiratory and metabolic demands may be particularly vulnerable to the consequences of inadequate energy delivery. In contrast, the association appeared weaker among patients who did not require mechanical ventilation, which may reflect lower overall illness severity and metabolic stress. While these findings should be interpreted cautiously, they reinforce the potential importance of prioritizing early nutritional adequacy, especially in mechanically ventilated patients with severe COVID-19.

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Discussion

In this retrospective cohort of critically ill patients with COVID-19, early energy deficit during the first week of ICU stay was independently associated with increased in-hospital mortality after adjustment for age and comorbidities. This finding is consistent with previous studies demonstrating that inadequate energy and protein delivery in critically ill COVID-19 patients is associated with poorer survival and a higher incidence of complications, underscoring the prognostic importance of early nutritional adequacy in high-risk populations (Compher et al., 2023; Hajimohammadebrahim-Ketabforoush et al., 2023; de Vries et al., 2021; Li et al., 2024; Silvah et al., 2024; van Zanten et al., 2023). Adequate nutritional support during the acute phase of illness is considered essential to maintain metabolic stability, preserve lean body mass, and support recovery among critically ill patients (Barazzoni et al., 2020; Singer & Thibault, 2026). Therefore, failure to achieve nutritional targets during the early ICU period may contribute to worsening clinical outcomes and increased mortality in severe COVID-19 cases.

Our results are biologically plausible in light of the hypermetabolic and catabolic responses commonly observed in severe COVID-19 infection. Critically ill patients frequently experience sustained elevations in resting energy expenditure and progressive underestimation of nutritional requirements when standard predictive equations are used, which can lead to unrecognized cumulative energy deficits during ICU treatment (Whittle et al., 2025; Niederer et al., 2024; de Waele et al., 2021). Inflammatory activation, prolonged immobilization, and respiratory distress further intensify muscle protein breakdown and metabolic demands in this population (Yu et al., 2021). As a result, inadequate nutritional intake can accelerate skeletal muscle wasting, impair respiratory muscle function, prolong mechanical ventilation, and increase susceptibility to ICU-acquired weakness and mortality (Compher et al., 2023; Silvah et al., 2024). These mechanisms support the observed association between early energy deficit and adverse outcomes in critically ill COVID-19 patients.

Although protein deficit was not significantly associated with mortality in our adjusted models, the direction of the observed effect aligned with previous studies suggesting that higher protein intake may improve outcomes in critically ill patients, including those with severe COVID-19 (Compher et al., 2023; Hajimohammadebrahim-Ketabforoush et al., 2023; Silvah et al., 2024; Heyland et al., 2025; de Vries et al., 2021). Adequate protein provision is important for preserving muscle mass, supporting immune function, and limiting catabolic deterioration during prolonged critical illness. The lack of statistical significance in the present study may be related to the relatively limited sample size, variability in timing and accuracy of intake assessment, and differences in cutoff values used to define protein adequacy. In addition, heterogeneity in disease severity and metabolic responses among ICU patients may have reduced the ability to detect a stronger independent association between protein deficit and mortality.

The observed tendency toward a stronger association between nutritional deficits and mortality among patients with ARDS and those requiring mechanical ventilation is consistent with the underlying pathophysiology of severe respiratory failure. ARDS is characterized by severe hypoxemia, increased ventilatory workload, systemic inflammation, and heightened metabolic stress, all of which may amplify energy expenditure and worsen the clinical consequences of underfeeding (Martindale et al., 2025; Ochoa et al., 2023). Patients with ARDS also frequently require prolonged ventilatory support and deep sedation, which can interfere with enteral nutrition delivery and the achievement of nutritional targets (Barazzoni et al., 2020;

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Ochoa et al., 2023). Although the interaction terms between ARDS and both energy and protein deficits did not reach statistical significance, the effect estimates consistently suggested greater harm among more severely ill patients. This finding is clinically plausible and may reflect limited statistical power, as interaction analyses generally require larger sample sizes and greater event numbers to reliably detect effect modification.

From a clinical perspective, these findings support current recommendations emphasizing early, individualized, and closely monitored nutrition therapy in critically ill COVID-19 patients (Barazzoni et al., 2020; Singer & Thibault, 2026; Thibault et al., 2023; Martindale et al., 2025). In practice, nutritional management should include systematic assessment of nutrition risk, regular monitoring of cumulative energy and protein delivery, and timely intervention when nutritional targets are not achieved (de Vries et al., 2021; van Zanten et al., 2023). Supplemental parenteral nutrition may need to be considered in patients with persistent enteral feeding intolerance, especially among those with ARDS or prolonged mechanical ventilation (Elke et al., 2024; Ochoa et al., 2023). Furthermore, because predictive equations may underestimate actual energy expenditure in severe COVID-19, more accurate approaches such as indirect calorimetry should be considered when available to minimize underfeeding and cumulative nutritional deficits (de Waele et al., 2021; Whittle et al., 2025; Niederer et al., 2024).

This study has several strengths, including the use of a well-defined cohort, consecutive patient sampling, quantification of cumulative nutritional deficits during the first seven ICU days, and formal assessment of ARDS as a potential effect modifier. However, several limitations should also be acknowledged. The retrospective single-center design limits causal inference and may introduce selection bias, information bias, and residual confounding despite statistical adjustment. Nutritional deficits were estimated using guideline-based calculations rather than direct measurements of energy expenditure, which may have resulted in misclassification of nutritional adequacy. The relatively limited sample size may also explain the absence of statistically significant interaction effects between ARDS and nutritional deficits. Finally, because the study was conducted during the early phase of the COVID-19 pandemic, the generalizability of these findings to later variants, evolving ICU practices, or different healthcare settings may be limited (Yang et al., 2024; Auld et al., 2023).

Future studies should validate these findings using larger multicenter cohorts and prospective designs to better clarify the relationship between nutritional deficits and mortality in critically ill COVID-19 patients. Further investigation is needed to determine how disease severity, ARDS, and mechanical ventilation influence the effectiveness of nutrition therapy in different patient subgroups, including those at highest nutritional risk (Heyland et al., 2025; Zhao et al., 2025; van Zanten et al., 2023). Randomized clinical trials stratified by nutrition risk and respiratory severity may help identify which patients benefit most from more aggressive early energy and protein delivery strategies. In addition, mechanistic studies examining inflammation, substrate utilization, metabolic adaptation, and muscle wasting may deepen understanding of how nutritional therapy influences outcomes in COVID-19-related ARDS and critical illness (Singer & Thibault, 2026; Martindale et al., 2025).

CONCLUSION

This study demonstrated that early energy deficit during the first week of ICU admission independently predicted higher mortality among critically ill COVID-19 patients. In contrast, protein deficit showed a consistent association with mortality but did not reach statistical

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significance in the present analysis. Although interaction analyses did not reveal a statistically significant modifying effect of ARDS, the observed directional trends suggested that patients with severe respiratory failure may experience greater nutritional vulnerability. These findings indicate that inadequate nutritional intake during the acute phase of critical illness may contribute to poorer clinical outcomes in COVID-19 patients treated in the ICU.

The findings of this study reinforce the importance of implementing early and individualized nutrition therapy in critically ill COVID-19 patients. Systematic monitoring and optimization of energy and protein delivery should be prioritized, particularly in patients with severe disease and high nutritional risk. Appropriate nutritional management may help reduce complications, preserve metabolic stability, and improve survival outcomes during intensive care treatment. Furthermore, multicenter prospective studies are urgently needed to determine optimal nutritional targets based on disease severity and to identify patient subgroups that may benefit most from aggressive early nutrition strategies.

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