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ORIGINAL RESEARCH

The Impact of Early Protein Advancement in Critically Ill Patients with COVID-19: A Multicenter Cardinality Matching Study

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Background: Limited evidence is available regarding the safety and effectiveness of early high protein intake in critically ill patients with COVID-19. Therefore, this study aims to assess the safety of early protein advancement during nutritional support in these patients.

Methods: A multi-center retrospective cohort study included adult critically ill patients with COVID-19 admitted to Intensive Care Units (ICUs) at three centers in Saudi Arabia. Patients were grouped into two groups based on the protein intake at day three of feeding initiation into low protein (≤0.8 mg/kg/day) versus high protein (>0.8 mg/kg/day) groups. Acute kidney injury (AKI) during the ICU stay was the primary endpoint, while the remaining were considered secondary endpoints.

Results: The study included 466 patients, but after cardinality matching with a 2:1 ratio, 192 were in the lower protein group compared with 96 patients in the high protein group. The rate of AKI was low in the highprotein group compared with the low protein group on day three of feeding initiation (19.9% versus 12.7%); however, this was not statistically significant (OR 0.54; 95% CI 0.26, 1.33; p=0.2). Additionally, patients in the high protein group had a higher rate of atrial fibrillation than those in the low protein group (OR 2.33; 95% CI 1.18, 4.62; p=0.02). No differences were observed in 30-day and in-hospital mortality (HR1.33, 95% CI 0.91, 1.96; p=0.14 and HR 1.21, 95% CI: 0.85, 1.72; p=0.29, respectively).

Conclusion: The advancement of protein in critically ill patients with COVID-19 was not associated with significant differences in the incidence of AKI. In contrast, the early advancement of protein in nutritional feeding within the first three days was associated with a higher incidence of atrial fibrillation.

Keywords: protein, nutrition, intensive care units, critically ill, COVID-19, SARS-CoV-2, acute kidney injury, AKI, mortality

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Introduction

Critically ill patients with COVID-19 are at increased risk of malnutrition. First, around 10% of patients with COVID-19 may present with gastrointestinal symptoms that negatively impact nutritional intake.[1] Second, the extremely high levels of inflammatory markers, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), lead to a cytokine release storm,[2,3] which increases nutritional needs and can generate a significant catabolic stress, increasing protein breakdown, muscle catabolism.[2,4,5] A meta-analysis found a pooled prevalence of malnutrition ranging from 31.5–94.4% among critically ill patients with COVID-19 .[6] Thishas been seen more in elderly patients with chronic diseases, such as type 2 diabetes, cancer, organ failure, or obesity (body mass index (BMI) ≥ 40 kg/m^2).[7] Malnutrition in patients with COVID-19 has been associated with a tenfold increase in mortality.[3,8] The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends that nutritional support (NS) be started within 24–36 hours of ICU admission or 12 hours of intubation in critically ill patients with COVID-19.[9] The advancement should occur gradually during the initial week of critical illness to fulfill energy goals of 15–20 kcal/kg actual body weight/day (70–80% of caloric requirements) and protein goals of 1.2–2.0 gm/kg actual body weight/day.[10] ASPEN also suggested a more individualized approach regarding protein prescription based on clinician judgment of the need of critically ill patients.[4] Conversely, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommended advancement to reach an energy goal of 27–30 kcal/kg body weight/day and protein ≥1g/kg body weight/day using the actual weight for non-obese patients and this advancement could be achieved slowly for selected patients.[4]

The impact of providing high versus low amounts of protein in the nutrition of critically ill patients, including those with COVID-19, on several clinical outcomes is an active area for research.[11,12] A prospective observational study reported that the administration of whey proteins in critically ill patients with COVID-19 was associated with reduced duration of MV and improved inflammatory status in ICU survivals.[13] The need for adequate protein intakes is essential to prevent muscle mass loss and promote adequate immune system.[5] High protein formula and protein derivatives can have direct anti-viral and anti-inflammatory effects in COVID 19.[13] A randomized control trial (RCT) reported that critically ill patients who received daily intravenous administration of amino acids starting on day 2 of ICU admission significantly improved the estimated glomerular filtration rate (eGFR) and daily urine output of patients on study day 4.[14] On the other hand, the EFFORT RCT, which investigated high protein dose (> 2.2 g/kg/day) versus usual dose administration within 96 hours in critically ill patients.[15] That study demonstrated that higher protein dose might be associated with negative outcomes for patients with acute kidney injury (AKI) and higher organ failure score.[15]

Acute kidney injury is a major concern in critically ill patients and is associated with an increased risk of in-hospital mortality and ICU length of stay.[16,17] Most AKI cases occur within the first 72 hours of ICU admission.[18] The risk of AKI is also high in patients admitted to the ICU with COVID-19.[19] One of the proposed mechanisms of kidney injury by COVID-19 is the direct viral injury in the angiotensin receptors, which are highly present in the kidney.[19] However, kidney function may be affected by other factors such as medications or nutrition.[20]

Various studies assessed the impact of NS on the clinical outcomes of critically ill patients with COVID-19.[15,19,21] Yet, the safety of early advancement of protein intake within the first three days in critically ill patients with COVID-19 remains under-explored. Therefore, our study aims to assess the safety of early protein advancement within NS in critically ill patients with COVID-19.

Methods

Study Design

This multi-center retrospective cohort study is related to the Saudi Critical Care Pharmacy Research (SCAPE) platform, which conducted several observational studies to evaluate the safety and effectiveness of treatments for critically ill patients.[22] King Abdullah International Medical Research Center (KAIMRC)—Institutional Review Board approved the study protocol in May 2022 (Ref.# NRC22R-196-04).

Study Setting

The study was conducted at three medical centers in different geographic distributions in Saudi Arabia. The study sites are detailed in the Supplemental File 1.

Study Participants

This study included adult (aged ≥ 18 years) critically ill patients admitted to the ICU from the participating sites with confirmed COVID-19 and receiving enteral nutrition (EN) through a feeding tube during ICU stay between March 1, 2020, and July 31, 2021. Patients were excluded if they had an ICU length of stay (LOS) ≤ one day, died within the first 24 hours of ICU admission, did not receive mechanical ventilation (MV) within 24 hours of admission, received total parenteral nutrition (TPN), or were designated as "Do-Not-Resuscitate" (Figure 1).

Data Collection

The Research Electronic Data Capture (REDCap®) platform hosted by the KAIMRC was used to manage and collect data, including demographic data, comorbidities, laboratory results, and outcomes. In addition, the protein content was determined using the specified formula (eg, Ensure Plus or Nephro Low Protein) measured in grams per milliliter. Following this, we calculated the total protein intake by multiplying the concentration by the hourly input amount. The details of the collected data can be found in Supplemental File 1.

Study Outcomes

The primary endpoint was AKI during the ICU stay post-day three of EN initiation. The secondary endpoints were re-feeding syndrome at day three of EN initiation, ICU complications such as liver injury and new-onset Atrial fibrillation (Afib), LOS (ICU and hospital), MV duration, and mortality. Outcome definitions are presented in Supplementary File 1.

Statistical Analysis

We used cardinality matching after considering the relevant covariates, which included age, BMI, NUTRIC score[23], days from ICU admission to feeding initiation, BUN, best GCS, and vasoactive inotropic score within 24 hours of ICU

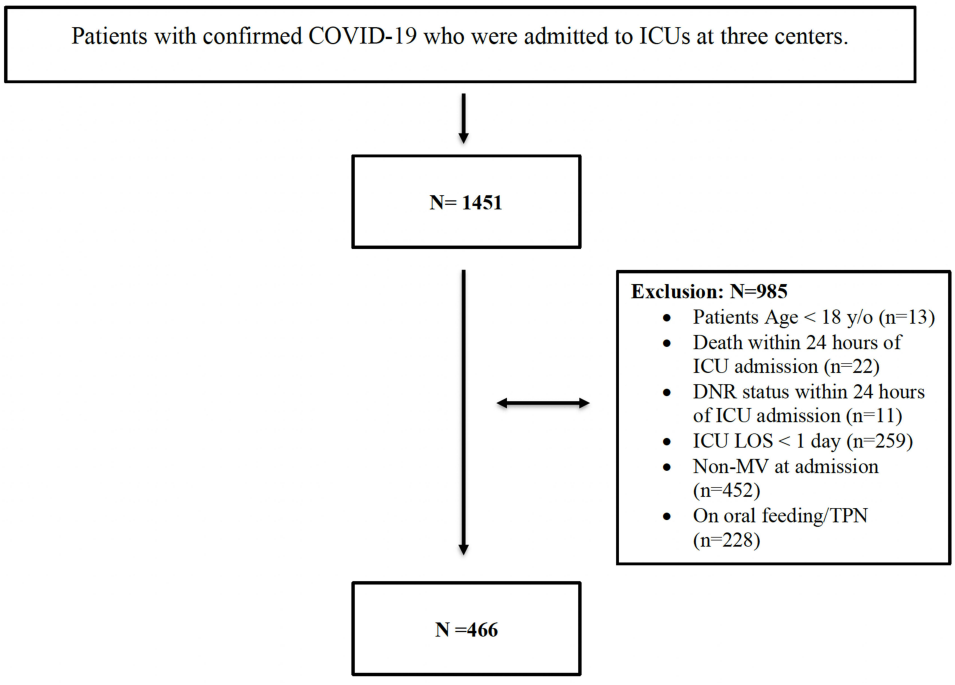

Figure 1 Flow diagram showing patients recruited with COVID-19.

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admission,[24] to find the largest matched sample that was balanced by solving a constrained linear integer programming problem, where the constraints enforced a given matching structure (2:1 rati) and pre-specified forms of covariate balance (exact matching) and the objective function maximized the total number of matched pairs. The detailed statistical analysis used to analyze the results were described in Supplementary File 1. The SAS software was used for all statistical analyses (SAS Version 9.4, SAS Institute Inc. Cary, NC, USA).

Results

Initially, our study included 466 critically ill patients with COVID-19 out of 1451 patients who were screened. At day 3 of feeding initiation, 353 patients (75.8%) received protein ≤ 0.8 g/kg/day (low protein group), while 116 patients received > 0.8 g/kg/day (high protein group). After cardinality matching with a 2:1 ratio, the lower protein group included 192 compared with 96 patients in the higher protein group. The median caloric intake on day 3 was 12.4 ± 5.54 Kcal/kg/day in the low protein group compared with 22.5 ± 4.34 Kcal/kg/day in the high protein group, as shown in Table 1.

Demographics and Clinical Characteristics

Most of the 466 study patients were males (60.3%) with a mean age of 63.5 ± 15.26 and a median BMI of 30.6 kg/m^2 (26.4, 36.1). The most observed comorbidities were hypertension (59.9%), diabetes mellitus (59.2%), dyslipidemia (26.6%), and chronic kidney disease (13.7%). Before cardinality matching, there were notable differences in baseline characteristics such as BMI, early Tocilizumab use within 24 hours of ICU admission, and Oxygenation Index, which were all significantly higher in the low protein group (Table 1). In contrast, patients in the high-protein group were older, had higher use of vasopressors and inotropes at admission, and exhibited elevated baseline d-dimer, INR and total bilirubin levels.

After applying cardinality matching, the variables of the two groups became comparable, except that patients in the low protein group had a higher rate of early Tocilizumab use within 24 hours.(Table 1). The median days of feeding initiation from ICU admission were one day in both groups and was not statistically significant.

Protein Intake and Caloric Consumption

On day three of starting enteral nutrition (EN), the median protein intake in the low protein group was 37.6 grams per day (with a range of 25.50 to 52.98 grams), compared to 67.3 grams per day (with a range of 60.20 to 72.45 grams) in the high protein group. Additionally, the median caloric intake on day three was 12.4 ± 5.54 Kcal/kg/day for the low protein group, while it was 22.5 ± 4.34 Kcal/kg/day for the high protein group. Furthermore, other nutritional components, such as carbohydrates and lipids, were significantly higher in the high protein group, as shown in Table 2.

AKI and Other Complications During ICU Stay

The crude analysis revealed that the rate of AKI was lower in patients in the high protein group compared with the low protein group at day three of feeding initiation (12.7% versus 19.9%; p=0.19). However, it was not statistically significant in crude analysis or logistic regression (OR 0.54; CI 0.26, 1.33; p = 0.2) (Table 3).

Patients in the high protein group on day 3 experienced a higher incidence of Afib compared to those in the low protein group. In the crude analysis, the incidence rates were 11.5% for the low protein group and 22.9% for the high protein group (p = 0.02). This finding was also supported by the regression analysis, which showed an odds ratio of 2.33 (95% CI: 1.18 to 4.62; p = 0.02). Other outcomes during the ICU stay, such as liver injury, aspiration, and refeeding syndrome risk at day 7, did not significantly differ between the two groups (Table 3).

In-Hospital and 30-Day Mortality

In the crude analysis both 30-day and in-hospital mortality were not significantly different (49% vs 59.2%; p = 0.15 and 55.6% vs 64.6%; p = 0.17, respectively). In addition, the multivariable Cox proportional hazards regression analyses reported no statistical significance between the two groups in 30-day and in-hospital mortality (HR 1.33, 95% CI 0.91, 1.96, p = 0.14 and HR 1.21, 95% CI 0.85, 1.72, p = 0.29, respectively) (Table 3).

Table 1 Summary of Demographics and Baseline Characteristics

Variable (s)	Before Matching				After Matching			
	Overall (N=466)	≤0.8 g/kg/day (N=353)	>0.8 g/kg/day (N=113)	P-value	Overall (N=288)	≤0.8 g/kg/day (N=192)	>0.8 g/kg/day (N=96)	P-value
Age (Years), Mean (SD)	63.5 (15.26)	62.7 (14.69)	65.9 (16.76)	0.0353*	64.7 (15.47)	63.9 (14.81)	66.4 (16.67)	0.1246*
Gender – Male, n (%)	281 (60.3)	208 (58.9)	73 (64.6)	0.2829^^	203 (70.5)	140 (72.9)	63 (65.6)	0.2009^^
BMI, Median (Q1,Q3)	30.6 (26.43, 36.09)	33.1 (28.04, 37.71)	26.5 (23.89, 29.78)	<0.0001*	28.1 (25.03, 31.38)	29.1 (25.97, 32.46)	26.2 (23.95, 29.57)	0.056*
Comorbidities								
Atrial fibrillation	21 (4.5)	14 (4.0)	7 (6.2)	0.3202^^	13 (4.5)	8 (4.2)	5 (5.2)	0.6881**
Hypertension	279 (59.9)	213 (60.3)	66 (58.4)	0.7152^^	170 (59.0)	113 (58.9)	57 (59.4)	0.9325^^
Diabetes Mellitus	276 (59.2)	211 (59.8)	65 (57.5)	0.6717^^	169 (58.7)	111 (57.8)	58 (60.4)	0.6722^^
Dyslipidemia	124 (26.6)	93 (26.3)	31 (27.4)	0.8198^^	72 (25.0)	45 (23.4)	27 (28.1)	0.3865^^
Heart Failure	37 (7.9)	28 (7.9)	9 (8.0)	0.9911^^	24 (8.3)	15 (7.8)	9 (9.4)	0.6511^^
Asthma	35 (7.5)	29 (8.2)	6 (5.3)	0.3078^^	17 (5.9)	12 (6.3)	5 (5.2)	0.7236^^
COPD	11 (2.4)	9 (2.5)	2 (1.8)	0.6347**	5 (1.7)	4 (2.1)	1 (1.0)	0.5235**
Ischemic heart disease	36 (7.7)	26 (7.4)	10 (8.8)	0.6071^^	25 (8.7)	17 (8.9)	8 (8.3)	0.8824^^
Chronic kidney disease	64 (13.7)	45 (12.7)	19 (16.8)	0.2744^^	45 (15.6)	28 (14.6)	17 (17.7)	0.4911^^
Cancer	20 (4.3)	15 (4.2)	5 (4.4)	0.9362**	14 (4.9)	10 (5.2)	4 (4.2)	0.6984**
Deep Vein Thrombosis	8 (1.7)	7 (2.0)	1 (0.9)	0.4342**	4 (1.4)	3 (1.6)	1 (1.0)	0.7218**
Pulmonary Embolism	4 (0.9)	3 (0.8)	1 (0.9)	0.9719**	4 (1.4)	3 (1.6)	1 (1.0)	0.7218**
Liver disease (any type)	12 (2.6)	10 (2.8)	2 (1.8)	0.5347**	7 (2.4)	6 (3.1)	1 (1.0)	0.2791**
Stroke	38 (8.2)	26 (7.4)	12 (10.6)	0.2713^^	27 (9.4)	18 (9.4)	9 (9.4)	>0.9999^^
APACHE II score, Median (Q1, Q3)	16.0 (11.00, 22.00)	16.0 (10.00, 22.00)	17.0 (11.00, 22.00)	0.4363^	17.0 (11.00, 22.00)	16.0 (10.50, 22.00)	17.0 (11.00, 21.50)	0.7690^
SOFA score, Median (Q1,Q3)	6.0 (4.00, 9.00)	6.0 (4.00, 9.00)	6.0 (4.00, 9.00)	0.7140^	6.0 (4.00, 9.00)	6.0 (4.00, 9.00)	6.0 (4.50, 9.00)	0.9272^
NUTRIC score, Median (Q1, Q3)	4.0 (2.00, 6.00)	4.0 (2.00, 6.00)	4.0 (3.00, 6.00)	0.2585^	4.0 (2.00, 6.00)	4.0 (2.00, 6.00)	4.0 (3.00, 6.00)	0.4096^
Early use of Tocilizumab within 24 hours, n (%)	177 (38.0)	145 (41.1)	32 (28.3)	0.0150^^	103 (35.8)	77 (40.1)	26 (27.1)	0.0298^^

(*Continued*)

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Table 1 (Continued).

Variable (s)	Before Matching				After Matching			
	Overall (N=466)	≤0.8 g/kg/day (N=353)	>0.8 g/kg/day (N=113)	P-value	Overall (N=288)	≤0.8 g/kg/day (N=192)	>0.8 g/kg/day (N=96)	P-value
Vasopressors, inotropes use at admission, n (%)	181 (39.0)	128 (36.5)	53 (46.9)	0.0479^^	108 (37.5)	69 (35.9)	39 (40.6)	0.4386^^
Serum creatinine (mmol/L) at admission, Median (Q1, Q3)	92.0 (68.00, 136.00)	92.0 (68.00, 135.00)	92.5 (68.00, 136.00)	0.9525^	96.5 (70.00, 150.00)	96.0 (70.00, 149.00)	99.0 (69.00, 152.00)	0.9455^
Blood Urea nitrogen (mmol/L) at admission, Median (Q1, Q3)	7.5 (5.00, 12.50)	7.2 (4.80, 12.20)	9.1 (5.40, 13.60)	0.0581^	8.1 (5.40, 13.50)	7.7 (5.35, 13.30)	9.4 (5.45, 13.70)	0.3873^
Oxygenation Index, Median (Q1, Q3)	17.7 (8.89, 27.88)	19.2 (10.45, 29.56)	11.3 (6.08, 21.81)	0.0012^	16.1 (7.42, 22.96)	17.5 (8.80, 25.95)	12.5 (6.22, 21.46)	0.0698^
Lactic acid (mmol/L) Baseline, Median (Q1, Q3)	1.7 (1.31, 2.63)	1.7 (1.31, 2.50)	2.0 (1.37, 2.89)	0.1174^	1.8 (1.31, 2.67)	1.7 (1.29, 2.50)	2.1 (1.40, 2.91)	0.0190^
Platelets count (10^9/L) Baseline, Median (Q1,Q3)	241.5 (186.00, 311.00)	246.2 (190.00, 318.00)	232.0 (177.00, 301.00)	0.1376^	244.5 (181.00, 320.00)	254.0 (190.00, 323.00)	226.0 (163.00, 300.00)	0.0605^
Total WBC Baseline, Median (Q1,Q3)	9.8 (6.54, 13.25)	9.7 (6.32, 13.05)	10.2 (7.49, 14.48)	0.0849^	10.1 (6.85, 13.20)	10.0 (6.41, 13.05)	10.3 (7.51, 14.10)	0.2907^
International normalized ratio, Median (Q1,Q3)	1.1 (1.00, 1.14)	1.1 (1.00, 1.14)	1.1 (1.02, 1.17)	0.0046^	1.1 (1.01, 1.14)	1.1 (1.00, 1.14)	1.1 (1.02, 1.15)	0.0717^
Activated partial thromboplastin time Baseline, Median (Q1,Q3)	29.1 (25.90, 32.70)	28.9 (25.70, 32.50)	30.4 (26.50, 33.30)	0.0531^	29.5 (25.95, 32.85)	29.1 (25.40, 32.60)	30.8 (26.50, 33.10)	0.1237^
Total bilirubin (umol/L), Median (Q1,Q3)	9.3 (6.80, 14.50)	9.0 (6.65, 13.05)	11.8 (7.40, 18.70)	0.0072^	10.0 (7.15, 15.85)	9.4 (7.00, 14.60)	12.0 (7.40, 18.90)	0.0788^
Alanine transaminase (U/l) at admission, Median (Q1,Q3)	35.0 (23.00, 60.00)	36.0 (24.00, 57.50)	34.0 (21.00, 67.00)	0.4600^	35.0 (23.00, 62.00)	36.0 (23.00, 59.00)	35.0 (23.00, 66.50)	0.7740^
Aspartate transaminase (U/l) at admission, Median (Q1,Q3)	51.0 (34.00, 75.00)	51.0 (34.00, 74.00)	53.0 (32.00, 77.00)	0.8071^	52.0 (33.00, 74.00)	50.0 (34.00, 74.00)	54.0 (32.00, 75.00)	0.6748^
Creatine phosphokinase baseline (U/l), Median (Q1,Q3)	177.5 (72.00, 540.00)	169.0 (68.00, 409.00)	238.0 (78.00, 717.00)	0.1018^	170.0 (70.00, 571.50)	160.0 (64.00, 483.00)	215.0 (77.00, 717.00)	0.1937^
C-reactive protein baseline (mg/l), Median (Q1,Q3)	133.0 (79.00, 203.00)	133.3 (82.00, 211.50)	123.0 (69.50, 183.50)	0.2147^	132.0 (79.00, 201.00)	132.0 (79.00, 208.00)	130.5 (86.00, 182.00)	0.5910^
D-dimer (mg/l) Level baseline, Median (Q1,Q3)	1.4 (0.72, 3.60)	1.3 (0.67, 3.38)	1.9 (0.90, 4.79)	0.0091^	1.6 (0.74, 3.92)	1.5 (0.70, 3.67)	2.0 (0.86, 5.33)	0.1006^

Ferritin Level (ug/l) baseline, Median (Q1,Q3)	765.4 (373.85, 2068.50)	728.8 (345.60, 1994.00)	862.9 (452.90, 2414.00)	0.1656^	823.0 (411.50, 2241.00)	785.5 (396.20, 2117.00)	905.5 (453.70, 2497.00)	0.2922^
Blood glucose level baseline (mmol/L), Median (Q1,Q3)	11.3 (7.70, 16.30)	11.4 (7.80, 16.70)	10.6 (7.70, 14.30)	0.2026^	10.8 (7.70, 15.60)	11.0 (7.70, 16.60)	10.6 (7.55, 14.00)	0.2002^
Albumin baseline (g/L), Median (Q1,Q3)	29.0 (26.00, 32.00)	29.0 (27.00, 33.00)	29.0 (25.00, 32.00)	0.1244^	29.0 (26.00, 32.00)	29.0 (26.00, 32.00)	29.0 (25.00, 32.00)	0.4843^
Highest heart rate at admission, Median (Q1,Q3)	106.0 (93.00, 120.00)	107.0 (93.00, 120.00)	105.0 (90.00, 120.00)	0.4428^	106.0 (92.50, 121.00)	107.5 (94.00, 121.50)	105.0 (88.50, 119.50)	0.2419^
Lowest MAP at admission, Median (Q1,Q3)	67.0 (58.00, 76.00)	68.0 (59.00, 77.00)	65.0 (58.00, 73.50)	0.1253^	67.0 (59.00, 77.00)	68.0 (59.00, 78.00)	64.0 (58.00, 73.50)	0.0831^
Patient received nephrotoxic drugs/material during ICU stay, n (%)*$	452 (97.0)	345 (97.7)	107 (94.7)	0.0990**	279 (96.9)	188 (97.9)	91 (94.8)	0.1508**
Days from ICU admission to feeding initiation, Median (Q1,Q3)	1.0 (0.00, 4.00)	2.0 (1.00, 4.00)	1.0 (0.00, 3.00)	0.0043^	1.0 (0.00, 3.00)	1.0 (0.00, 3.00)	1.0 (0.00, 3.00)	0.2823^
GRV at day 1 of starting nutrition (mL), Median (Q1,Q3)	40.0 (20.00, 117.50)	50.0 (20.00, 120.00)	30.0 (17.50, 85.00)	0.1869^	37.5 (20.00, 105.00)	40.0 (20.00, 120.00)	30.0 (17.50, 70.00)	0.3179^

Notes: *t-test/^ Wilcoxon rank sum test is used to calculate the P-value. ^^Chi-square test is used to calculate the P-value. **Fisher Exact test is used to calculate the P-value. *$^{\$}$Nephrotoxic medications and materials include intravenous (IV) contrast agents, colistin, vancomycin, gentamicin, amikacin, furosemide, and sulfamethoxazole/trimethoprim.

Abbreviations: COPD, Chronic obstructive pulmonary disease; BMI, Body Mass Index; WBC, White Blood Cell; GRV, Gastric Residual Volume.

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Table 2 Clinical Outcomes of Critically Ill Patients with COVID-19 After Matching

Variable (s)	Before Matching				After Matching			
	Overall (N=466)	≤0.8 g/kg/day (N=353)	>0.8 g/kg/day (N=113)	P-value	Overall (N=288)	≤0.8 g/kg/day (N=192)	>0.8 g/kg/day (N=96)	P-value
Total calorie at day 1 (kcal/kg/day), Mean (SD)	6.7 (4.86)	5.8 (3.90)	9.5 (6.29)	<0.0001*	7.4 (5.08)	6.5 (4.27)	9.0 (6.08)	0.0016^
Protein at day 1 of starting nutrition (g), Median (Q1,Q3)	19.4 (11.70, 28.40)	17.9 (10.00, 26.00)	24.5 (13.60, 37.50)	0.0001^	20.0 (11.70, 29.60)	18.6 (10.50, 26.80)	22.6 (13.37, 34.60)	0.0094^
Carbohydrates at day 1 of starting nutrition (g), Median (Q1,Q3)	40.8 (22.82, 63.00)	39.1 (22.80, 56.20)	49.9 (27.70, 73.65)	0.0002^	41.6 (23.60, 64.60)	38.9 (22.82, 61.00)	48.0 (26.08, 68.40)	0.0399^
Lipids at day 1 of starting nutrition (g), Median (Q1,Q3)	23.9 (13.10, 34.33)	22.3 (12.10, 31.90)	29.2 (16.50, 43.66)	0.0003^	25.0 (14.60, 36.80)	22.9 (12.50, 34.88)	28.9 (15.90, 39.24)	0.0497^
Total calorie at day 3 (kcal/kg/day), Mean (SD)	14.1 (6.75)	11.5 (5.13)	22.2 (4.36)	<0.0001*	15.8 (7.04)	12.4 (5.54)	22.5 (4.34)	<0.0001*
Protein at day 3 of starting nutrition (g/day), Median (Q1,Q3)	46.9 (30.10, 62.90)	39.7 (26.30, 55.00)	66.1 (60.19, 72.20)	<0.0001*	50.3 (32.15, 63.85)	37.6 (25.50, 52.98)	67.3 (60.20, 72.45)	<0.0001*
Lipids at day 3 of starting nutrition (g/day), Median (Q1,Q3)	54.8 (36.00, 78.00)	49.1 (33.80, 69.00)	80.0 (66.85, 91.28)	<0.0001*	59.8 (37.60, 79.80)	49.2 (31.44, 71.60)	81.8 (69.00, 91.56)	<0.0001*
Carbohydrates at day 3 of starting nutrition (g/day), Median (Q1,Q3)	99.8 (59.28, 131.20)	83.8 (52.95, 119.60)	130.4 (113.40, 144.70)	<0.0001*	104.8 (65.20, 136.90)	82.5 (51.30, 117.00)	132.1 (111.60, 145.15)	<0.0001*

Notes: *t-test/^ Wilcoxon rank sum test is used to calculate the P-value.

Table 3 Complications During ICU Stay After Matching

Outcomes	Protein on Day Three of Feeding Initiation		P-value	Adjusted Odds Ratio (95% CI)	P-value $
	≤0.8 mg/kg/day	>0.8 mg/kg/day			
Acute kidney injury post day#3 of nutrition initiation, n (%)β	26/105 (19.9)	9/62 (12.7)	0.19^^	0.59 (0.26,1.33)	0.20
New onset A fib., n (%)Δ	22 (11.5)	22 (22.9)	0.01^^	2.33 (1.18,4.62)	0.02
Liver injury, n (%)Δ	23 (12.0)	9 (9.4)	0.51^^	0.82 (0.35,1.91)	0.65
Refeeding syndrome risk at day#7, n (%)Δ	89 (59.7)	51 (68.9)	0.18^^	1.41 (0.764,2.583)	0.27
Aspiration at day#7, n (%)Δ	1 (0.7)	0 (0.0)	0.47**	NC	NC
Bowel movement at day#7, n (%)Δ	103 (68.7)	52 (68.4)	0.97^^	1.06 (0.57,1.96)	0.86
				Hazard Ratio (95% CI)	**P-value $***
30-day mortality, n (%)Δ	77 (49.0)	45 (59.2)	0.15^^	1.33 (0.91, 1.96)	0.14
In-hospital mortality, n (%)Δ	90 (55.6)	53 (64.6)	0.17^^	1.21 (0.85, 1.72)	0.29
				Beta coefficient (Estimates) (95% CI)	**P-value $****
MV duration (Days), Mean (SD)Δ	18.4 (13.91)	20.5 (32.16)	0.32^	0.16 (−0.04,0.37)	0.12
ICU Length of Stay (Days), Median (Q1,Q3)Δ	17.0 (11.00, 28.00)	15.0 (8.50, 23.00)	0.07^	−0.06 (−0.23,0.11)	0.31
Hospital Length of Stay (Days), Median (Q1,Q3)Δ	25.0 (15.00, 36.50)	21.5 (14.00, 35.00)	0.45^	−0.04 (−0.23,0.16)	0.73

Notes: β Denominator of the percentage is non-AKI within 24 hours of ICU admission. Δ Denominator of the percentage is the total number of patients. *T-Test / ^ Wilcoxon rank sum test is used to calculate the P-value. ^^Chi-square test is used to calculate the P-value. $ Logistic regression is used to calculate odds ratio and p-value. $* Cox proportional hazards regression analysis used to calculate hazard ratio and p-value. $** Generalized linear model is used to calculate estimates and p-value.
Abbreviations: A fib, Atrial fibrillation; MV, Mechanical ventilation; ICU, Intensive care unit; SD, Standard deviation; Q1, First interquartile; Q3, Third interquartile; NC, Not computable.

MV Duration and LOS

Patients in the high protein group had a non-significant longer MV duration in crude analysis (20.5 vs 18.4 days; p = 0.32) as well as regression analysis (beta coefficient: −0.16, 95% CI: [−0.04, 0.37], p = 0.12). Moreover, the ICU and hospital LOS were comparable between the groups (beta coefficient: −0.06, 95% CI (−0.23, 0.11); p = 0.51 and beta coefficient: −0.04, 95% CI: [−0.23, 0.16], p = 0.73, respectively) (Table 3).

Discussion

We aimed in our study to assess the safety of early protein advancement in critically ill patients with COVID-19. In the current study, higher protein intake on day three was associated with a marginally significant reduction in AKI. However, early protein advancement did not significantly impact 30-day mortality or in-hospital mortality among critically ill patients with COVID-19. Although the group with higher protein intake had slightly shorter stays in the ICU and hospital compared to the lower protein group, this difference was not statistically significant. Higher protein intake was linked to a significantly higher incidence of new-onset AFib, which warrants further investigation into electrolyte management and confounding factors like tocilizumab.

Higher protein intake on day three in critically ill patients with COVID-19 was associated with a marginally lower AKI occurrence compared to the low protein group. This finding is contrary to the EFFORT trial, a recently published RCT that aimed to investigate the impact of increased protein intake compared with lower protein on clinical outcomes among critically ill patients.[15] EFFORT trial found that higher protein dose might be associated with negative outcomes for patients with AKI and higher organ failure score.[15] The discrepancy in results could be attributed to differences in methodology and the included population in the studies.[15] In our study, > 0.8 g/kg/day was our cutoff to differentiate between high and low doses of protein, while in the EFFORT trial, 2.2 g/kg/day was the cutoff for high doses of

protein.[15] Also, our population was mainly critically ill patients with COVID-19 while in the EFFORT trial, COVID-19 patients were only 85 (6.5%) patients. However, our findings related to the positive impact of protein on kidney function are consistent with a previous Phase 2 RCT that evaluated the role of IV amino acids in critically ill patients.[14] The trial found a significant improvement in eGFR and urine output with IV amino acid therapy compared with standard care in critically ill patients although the duration of kidney dysfunction did not differ between two groups.[14] In our study, the interesting finding of a lower rate of AKI among the higher protein group might result from some baseline characteristics. To mitigate this, we performed cardinality matching, such that the prevalence of CKD, baseline serum creatinine, and use of nephrotoxic agents were balanced between the study groups. Nevertheless, more studies are needed to validate the potential benefit of higher protein provision on kidney function among critically ill patients with COVID-19.[25]

The advancement of nutrition could be limited by factors including refeeding syndrome and feeding intolerance. In our study, providing protein higher than 0.8 g/kg/day on the third day of nutrition initiation resulted in similar refeeding syndrome risk between the two groups. In contrast, shariatpanahi et al found that the hazard ratio of refeeding syndrome was reduced by 90% with increased protein intake among critically ill patients with COVID-19 who were at risk of refeeding syndrome.[21] A possible explanation for this might be that the time frame for documenting the outcome was different between our study and Shariatpanahi's study. We reported the risk of refeeding syndrome on day 7, while the shariatpanahi's trial reported the risk within the first 5 days of nutrition provision. Additionally, the mean actual protein intake in the shariatpanahi's trial was 0.59 g/kg/day in patients who did not develop refeeding syndrome compared with 0.52 g/kg/day in patients who experienced refeeding syndrome.[21] Both means of protein dose were lower than our cutoff of 0.8 g/kg/day.

In our study, Higher protein intake on day three of nutrition initiation did not affect any of the mortality outcomes. A meta-analyses in critically ill patients showed no benefit of protein doses >1 g/kg/day.[25] The inconsistency may be due to the weight used for calculating protein dose. We used actual body weight as recommended by several guidelines, while Silvah et al used ideal body weight for protein dosing. Furthermore, some biomarkers of hypoproteinemia, such as albumin and BUN, could predicate disease outcomes in COVID-19 patients, including mortality.[26] In our study, albumin and BUN were balanced between the two groups. This could explain the neutral effect of early advancement of protein on mortality that we found in our study. Also, the early administration of tocilizumab may have confounded our findings regarding mortality. Even after matching, 40% of patients in the lower protein group received an early dose of tocilizumab compared with only 27% of patients in the higher protein group. The use of IL-6 inhibitors, such as tocilizumab, was linked to a mortality benefit in hospitalized COVID-19 patients compared to usual care or placebo.[27] However, our findings regarding the effect of protein on mortality align with those observed in critically ill patients in general.[28] A meta-analysis investigated the effect of protein delivery on several clinical outcomes in critically ill patients and found that a protein dose higher than 1g/kg/day showed no mortality benefits.[28] Another meta-analysis in general critical care patients that used a cutoff of 1.2 g/kg/day for protein reported the same neutral finding of higher protein on mortality outcomes.[23,24,29–36]

In the context of severely ill patients, the heightened catabolic state leads to the complete utilization of all protein administered to these patients, implying that protein supplementation has minimal impact on meeting their caloric needs. Post hoc analysis of the Permit trial showed that lower and higher protein groups were associated with similar 90-day mortality.[37] Similarly, the ANZICS trial revealed no significant difference in 90-day mortality between critically ill patients who received calorie-dense nutrition and those who received the standard of care.[38,39] However, multiple studies found short- and long-term outcomes worse after receiving higher protein intake during the first few days of nutritional supplementation.[35,36]

Our study found shorter LOS in the higher protein group, though not statistically significant. Our finding is consistent with generally critically ill patients receiving enteral nutrition, as Lee, Zheng-Yii et al 2021 reported.[28,29] Furthermore, hospital LOS was comparable between both groups and consistent with the literature.

There is a strong relation between new-onset A fib and increased mortality and morbidity in COVID-19 patients.[30,31] In the current study, the higher protein group had a higher new-onset A-Fib incidence compared with the lower protein group. In our study, the odds of refeeding syndrome after one week of nutrition initiation were higher among patients who received high protein, although it was not statistically significant. Therefore, it may be possible that patients in the

higher protein intake group experienced hypokalemia and hypomagnesemia, which are both known causes of cardiac arrhythmia.[32] Also, the higher percentage of tocilizumab use in patients in the lower protein group could be another possible explanation for the high incidence of new-onset Afib. To date, few studies hypothesized that IL-6 inhibitors, including tocilizumab, could mitigate the high arrhythmic risk associated with severe COVID-19.[33,34] The current Nutritional Guidelines did not address certain outcomes related to the timing of dietary advancements within three days and the variety of outcomes studied. There is a pressing need for further research to explore the association between early protein intake advancement and the increased incidence of new-onset Afib.

Our study has some limitations. The first limitation is related to the nature of the study, which is a retrospective study with a relatively small sample size. Nevertheless, we utilized cardinality matching to minimize the bias and create a balance between the two groups. Second, the median NUTRIC score in our study makes these findings less generalizable to patients with a high risk of malnutrition and may benefit more from aggressive nutrition provision. Third, we did not evaluate muscle outcomes that may be affected by higher protein intake. Further studies are recommended to assess the long-term effect of higher protein intake on several outcomes, especially among critically ill COVID-19 survivors.

Conclusion

The advancement of protein on day three of feeding initiation in critically ill patients with COVID-19 was not associated with a significant difference in the incidence of AKI, 30-day and in-hospital mortality, and other ICU-related complications. However, early advancement of protein intake was associated with a higher incidence of Afib. The findings of this study should be interpreted cautiously due to its limitations. Further large prospective observational studies and RCTs are necessary to validate these findings.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Informed Consent Statement

The study protocol was reviewed and approved by the Institutional Review Board of King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia, in May, 2022 (Ref.# NRC22R-196-04). The study was conducted in accordance with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (adopted 1964; updated 2013), national ethical regulations, and local institutional guidance of study centers. Informed consent from the study patients was waived due to the retrospective observational nature of the study. All patient's information was accessed and maintained with strict confidentiality, ensuring compliance with data protection regulations and institutional policies.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest.

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