Clinical Nutrition ESPEN 45 (2021) 507–510

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Short Communication

Protein provision and lower mortality in critically ill patients with COVID-19

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A R T I C L E I N F O

Article history:
Received 29 June 2021
Accepted 4 July 2021

Keywords:
COVID-19
Nutritional therapy
Tube feeding
Mortality
Critical care
Protein supply

S U M M A R Y

Background and aims: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) severely impacted the management of critically ill patients, including nutritional therapy. This study aimed to verify an association between mortality and the energy and protein provided to critically ill patients affected by the SARS-CoV-2 and receiving enteral nutrition support.
Methods: Patients with confirmed COVID-19, with >7 days of stay in the ICU, on enteral nutrition were followed from the moment of hospitalization until discharge from the ICU or death. Data about age, gender, Simplified Acute Physiology Score III (SAPS3), intensive care unit (ICU) length of stay, days on mechanical ventilation (MV), clinical endpoint outcome (discharge or death), and daily energy and protein provision were collected from electronic medical records. Cox regression analyses and Kaplan-Meyer curves were used in statistical analysis.
Results: Fifty-two patients (66.2 ± 13.1 years; 53.8% women) were enrolled in the present study. The mean length of hospitalizations and SAPS3 score were 17.8 ± 9.8 days and 78.7 ± 14.7, respectively; all patients needed mechanical ventilation (mean of days was 16.42 ± 9.1). For most patients (73.1%) the endpoint was death. Twenty-five percent of patients had protein supply >0.8 g/IBW/day. Survival during COVID-19 hospitalization at ICU was significantly different among patients according to protein supply ($p = 0.005$). Hazard Ratios (HR) for protein supply showed that a protein intake >0.8 g/IBW/day was associated with significantly lower mortality (HR 0.322, $p = 0.049$).
Conclusion: Our study suggests that a protein supply at least > 0.8 g/IBW/day could be related to reduced mortality in ICU patients with COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has severely impacted the management of critically ill patients and individualized nutrition therapy (NT) should be an integral part of the patient's treatment [1,2]. For those patients that can be fed orally, some authors recommended a personalized meal combined with oral supplements [3]. For patients that oral intake is not possible, guidelines suggested specific enteral/parenteral nutrition formulas [2] with low glucose and high protein content [4]. Moreover, considering evidence showing that malnutrition delays healing times and increases the number of hospitalizations days [2], prevention, diagnosis, and treatment of under-nutrition or nutritional risk must be regularly included in the management of hospitalized COVID-19 patients [1,2]. Therefore, it is a general acknowledgment that mortality can be reduced substantially by optimal nutrition utilization [5]. Underestimating the importance of adequate NT is an error that can dramatically affect both outcome and prognostics. This study aimed to verify if there is an association between mortality rate and the amount of energy and

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https://doi.org/10.1016/j.clnesp.2021.07.005
2405-4577/

protein provided to critically ill patients with SARS-CoV-2 and receiving enteral nutrition support.

2. Methods

This observational retrospective study analyzed data collected between March and December 2020 from a hospital served by the governmental central health system. From all adult patients infected by the SARS-CoV-2 (all confirmed by real-time PCR) and admitted to the intensive care unit (ICU), we enrolled those who remained hospitalized for more than 7 days and were in use of enteral nutrition. Age <18 years, pregnancy, use of oral feeding or parenteral nutrition, and missing data regarding NT were used as exclusion criteria. From the moment of hospitalization until their outcome (endpoint: death or discharge), all patients were followed by the NT team. This study was conducted according to the Declaration of Helsinki and was approved by the local ethics committee (number 11762).

Data on basic information [age, gender, height, and ideal body weight (IBW)], the Simplified Acute Physiology Score III (SAPS3), ICU length of stay, days on mechanical ventilation (MV), discharge from the hospital or death (endpoint final clinical outcome), and daily energy and protein supplies were collected from electronic medical records.

NT was provided according to the institutional policy, which was based on the current guidelines for COVID-19 patients [2,4]. Patients received NT as early as possible since hemodynamic and ventilatory conditions allowed it, in line with the intensive care unit team. Gastric positioning of tube feeding was not a reason to delay enteral nutrition delivery. Infusion method was continuous. Generally, an enteral nutrition formula with 75 g of protein/L and 1.5 kcal/mL was used. Protein modules (whey) were administered when necessary, according to the patient's needs. For nutritional support assessment, total energy and protein provided were divided by IBW and by the days of ICU hospitalization.

Data are presented as mean and standard deviation or in frequency rate (%). Cox regression analyses were performed using the length of ICU stay as the time variable; death as outcome variable; and the average energy and protein/IBW or actual weight/day as the independent variable. Among the possible covariates (age, sex, days on MV and SAPS3 score), only those with $p < 0.05$ by univariate analysis were included in the final multivariate model. Hazard ratios (HRs; 95% confidence interval) were adjusted for age, SAPS3 score and days on MV. Kaplan–Meier survival function was used to estimate mortality (mortality and discharge were coded as events and censoring, respectively). Significance level was set at $p < 0.05$ (SPSS, Version 20.0, IL).

3. Results

Fifty-two patients (mean age, 66.2 ± 13.1 years; 53.8% women) were enrolled in the present study. The mean IBW was 69.7 ± 7.7 kg and the mean length of hospitalization was 17.8 ± 9.8 days. All patients needed mechanical ventilation (mean of days was 16.42 ± 9.1). The SAPS3 score was 78.7 ± 14.7. Considering the outcome, most patients (73.1%, n = 38) died.

The mean daily protein and energy supplied during the hospitalization period were 0.6 ± 0.3 g/IBW/day (0.1–1.84 g/IBW/day) and 9.1 ± 6.3 kcal/IBW/day (0.94–36.8 kcal/IBW/day), respectively.

Alone, age (HR 1.043, p = 0.006) and SAPS3 score (HR 1.030, p = 0.037) were associated with higher mortality rates; however, days on VM (HR 0.782, p = 0.000) and protein supply (HR 0.284, p = 0.010) were associated with lower mortality rates. The multivariate analysis results are shown in Table 1. The HRs for protein supply showed that a protein intake >0.8 g/IBW/day was associated with significantly lower mortality (HR 0.322, p = 0.049). No association was found between final clinical outcome and energy supply.

Twenty-five percent (n = 13) of patients had protein supply > 0.8 g/IBW/day. The Kaplan–Meier survival analysis showed that survival during COVID-19 hospitalization at ICU was significantly different among patients according to protein supply, with rates of 15.4% among patients with protein supply <0.8 g/IBW/day and 61.5% among those with protein supply >0.8 g/IBW/day (p = 0.005; Fig. 1).

4. Discussion

This study suggests a possible association between protein provided by enteral nutrition and mortality in critically ill patients with COVID-19. Some previous studies also evidenced that the achievement of protein requirements in ICU patients resulted in lower mortality [5,6].

Some authors suggest a positive association between metabolic/nutrition issues including obesity, hyperlipidemia, and diabetes with severe COVID-19 disease [7]. Furthermore, malnutrition and nutritional risk are related to a worse clinical prognosis mainly in severely ill patients and may impair the outcome [8]. Considering COVID-19 patients, sarcopenia has been speculated to be related to worse prognosis [9]. Zhao et al. (2020) [10] observed a positive correlation between high nutritional risk and adverse clinical results of COVID-19.

Based on this point, adequate protein intake should be achieved to prevent muscle mass loss and promote adequate immune response [9]. Despite all efforts, the amount of protein and energy offered to patients were less than previously recommended and prescribed by the NT team. Patients with COVID-19 were kept in prone positioning frequently, and in trophic enteral nutrition in the initial days. Also, several factors affected the provision of nutritional therapy, such as lack of professionals, workload, and severity of disease, resulting in a great number of pauses in the infusion of enteral feeding.

Our study suggests that a protein supply at least >0.8 g/IBW/day could be related to reduced mortality in ICU patients with COVID-

Table 1
Cox regression analysis for mortality rate in critical COVID-19 patients (n = 52).

Variable	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Mortality rate				
Age (years)	1.04 (1.00–1.08)	0.006	0.99 (0.97–1.03)	0.959
Sex	0.87 (0.46–1.67)	0.678	–	–
Days on MV	0.78 (0.72–0.85)	0.000	0.75 (0.69–0.83)	0.000
SAPS3	1.03 (1.01–1.06)	0.037	1.02 (0.99–1.05)	0.224
Energy intake (kcal/IBW/day)	0.94 (0.88–1.00)	0.092	–	–
Protein >0.8 g/IBW/day	0.28 (0.11–0.74)	0.010	0.32 (0.10–0.99)	0.049

MV: mechanical ventilation; SAPS3: Simplified Acute Physiology Score III; IBW: ideal body weight; HR: Hazard ratios; CI: confidence interval.

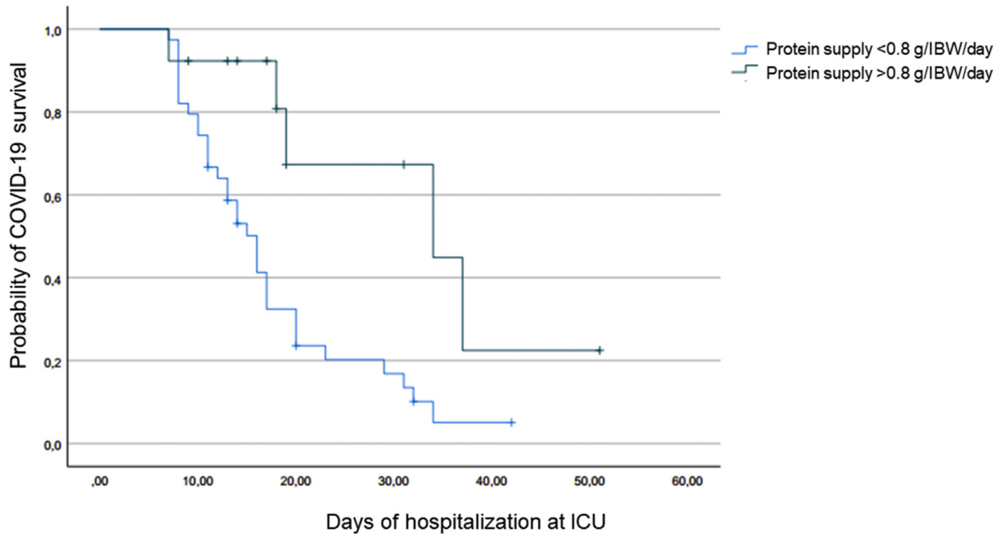

Fig. 1. Kaplan–Meier survival curves from Intensive Care Unit (ICU) patients with COVID-19, according to protein supply. IBW: ideal body weight.

19. This result was independent of total calories offered to these patients and of the SAPS3 score (severity of illness). Thus, in this case, protein appears to be more important than energy supply to survival. Considering that most of the patients didn't reach the amount of protein/kg recommended by the current guidelines (~>1.2 g/kg/day), we choose for the cutoff point the lowest possible value to differentiate between surviving and non-surviving patients. Other authors evidenced the importance of dietary protein intake, particularly for critical patients who depend on enteral nutrition [9]. The inflammatory reaction due COVID-19 infection, mainly characterized by higher levels of interferon-a, IL-6, IL-12, tumor necrosis factor-a, C-reactive protein, and monocyte chemotactic protein-1, may elevate metabolic stress and muscle catabolism [11]. Adequate nutritional support, especially protein supply, can promote skeletal muscle mass preservation and benefit the treatment of COVID-19 disease [6].

Considering that recent reference about COVID-19 nutritional goals was based on IBW [12] and that in some situations the actual weight was not possible to be obtained after admission or it was clearly not accurate (due to some degree of edema or other situations that was not possible to rule out), IBW was considered in the analysis.

Adequacy of nutritional therapy should be emphasized, since it seems to improve clinical outcomes of patients infected by SARS-CoV-2. Thus, adherence to recommendations should be a key point of nutritional care, and every effort should be made to avoid underfeeding, overfeeding, but providing adequate amounts of protein. Furthermore, despite our significant results with a protein supply >0.8 g/IBW/day, the authors speculate that higher protein provisions (as stated in clinical guidelines [2,4]) could be related to additional benefits, and should be pursued.

As a limitation, due to the inclusion factors applied (only patients receiving enteral nutrition, with at least 7 days of ICU hospitalization, with SAPS3 score available and with COVID-19 confirmed by PCR test), a small number of patients were evaluated. However, important results were found after adequate statistical analysis.

5. Conclusion

In conclusion, our study suggests that a protein supply at least >0.8 g/IBW/day could be related to reduced mortality in ICU patients with COVID-19. Adequate nutritional support should be considered one of the top priorities of COVID-19 patient's care.

Funding sources

This research received no specific external funding.

Statement of authorship

JHS, CMML, SFCC and JSM contributed to the conception and design of the research; ACB and GPJ performed data collection; JHS and CFN contributed to the analysis and interpretation of the data; JHS and CFN wrote and drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final version.

Declaration of competing interest

All authors declare no conflicts of interest.

Acknowledgements

Special thanks to Maira de Freitas Coelho Ferreira and Luciano Donizete Rodrigues.

References

[1] Brugliera L, Spina A, Castellazzi P, Cimino P, Tettamanti A, Houdayer E, et al. Rehabilitation of COVID-19 patients. J Rehabil Med 2020;52(4). jrm00046.
[2] Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV2 infection. Clin Nutr 2020;39(6):1631–8.
[3] Cintoni M, Rinninella E, Annetta MG, Mele MC. Nutritional management in hospital setting during SARS-CoV-2 pandemic: a real-life experience. Eur J Clin Nutr 2020;74:846–7.
[4] Martindale R, Patel JJ, Taylor B, Warren M, McClave SA. Nutrition therapy in the patient with COVID-19 disease requiring ICU care [Internet]. 2020 [cited 2020 Apr 10]. Available from: www.nutritioncare.org. https://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/NutritionTherapyCOVID-19_SCCM-ASPEN.pdf.
[5] Weijs PJ, Stapel SN, de Groot SD, Driessen RH, de Jong E, Girbes ARJ, et al. Optimal protein and energy nutrition decreases mortality in mechanically

ventilated, critically ill patients: a prospective observational cohort study. JPEN - J Parenter Enter Nutr 2012;36:60–8.
[6] Song JH, Lee HS, Kim Sy, Kim EY, Jung JY, Kang YA, et al. The influence of protein provision in the early phase of intensive care on clinical outcomes for critically ill patients on mechanical ventilation. Asia Pac J Clin Nutr 2017;26(2):234–40.
[7] Parveen R, Sehar N, Bajpai R, Agarwala NB. Association of diabetes and hypertension with disease severity in covid-19 patients: a systematic literature review and exploratory meta-analysis. Diabetes Res Clin Pract 2020:108295.
[8] Sharma K, Mogensen KM, Robinson MK. Pathophysiology of critical illness and role of nutrition. Nutr Clin Pract 2019;34(1):12–22.
[9] Wang P, Li Y, Wang Q. Sarcopenia: an underlying treatment target during the COVID-19 pandemic. Nutrition 2021;84:111104.
[10] Zhao X, Li Y, Ge Y, Shi Y, Lv P, Zhang J, et al. Evaluation of nutritional risk and its association with mortality risk in severe and critically III COVID-19 patients. JPEN - J Parenter Enter Nutr 2020;2020:1–11.
[11] Meftahi GH, Jangravi Z, Sahraei H, Bahari Z. The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-aging. Inflamm Res 2020;69:825–39.
[12] Whittle J, Molinger J, MacLeod D, Haines K, Wischmeyer PE, LEEP-COVID Study Group. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. Crit Care 2020;24(1):581.