The association between enteral feeding with survival of critical patients with COVID-19 patients

Maryam Gholamalizadeh[1], Zahra Salimi[2], Khadijeh Abbasi Mobarakeh[3], Zahra Mahmoudi[4], Shirin Tajadod[5], Mehdi Moosavi[4], Farkhondeh Alami[6], Bojlul Bahar[7], Saeid Doaei[1], Sara khoshdooz[8], Masoume Rahvar[8], Somayeh Gholami [8], and Masoume Pourtaleb[8]

[1]Shahid Beheshti University of Medical Sciences
[2]Ahvaz Jundishapur University of Medical Sciences
[3]Isfahan University of Medical Sciences
[4]Hamadan University of Medical Sciences
[5]Iran University of Medical Sciences
[6]Urmia University of Medical Sciences
[7]University of Central Lancashire
[8]Guilan University of Medical Sciences

January 30, 2024

Abstract

Background: Coronavirus disease 2019 (COVID-19) results in several complications and mortality in ICU patients. The effect of enteral nutrition on the survival of COVID-19 patients in the ICU has been investigated in limited instances. The aim of this study is to investigate the association of enteral feeding with biochemical and pathological indices associated with mortality in COVID-19 patients. Methods: This case-control study was conducted on 240 patients with COVID-19 hospitalized in the ICU including 120 eventually dead patients as the cases and 120 discharged patients as the controls. All of the patients received enteral nutrition. Data on general information, anthropometric measurements, and the results of lab tests were collected. Results: The recovered patients received significantly more high protein (60.8% vs. 39.6%, P=0.004) and high volume (61.6% vs. vs. 42.3%, P=0.005) formula compared to the dead patients. Mortality was inversely associated with high volume (OR:0.45 CI95%, P=0.008) and high protein formula (OR:0.42 CI95%, P=0.003). The results remained significant after adjusting for age and sex. Further adjustment for underlying diseases and smoking, BMI, and APACHII did not change the results. Conclusion: The findings of the study showed that there was a significant inverse association between mortality and high volume and high protein formula in COVID-19 patients that warrants further investigation.

Introduction

Coronavirus disease 2019 (COVID-19) is a new respiratory disease that first appeared in Wuhan, China (1). The COVID-19 disease has killed more than 5 million people globally (2) and has affected the lives of millions of people around the world due to the quarantine of cities, business closures, and social distancing (3). COVID-19 is associated with many health problems. One of these important complications is severe acute respiratory syndrome (4). Since the outbreak of this contagious disease, the number of cases has increased rapidly and it has affected all age groups and people all over the world (5). COVID-19 patients hospitalized in the ICU often need mechanical ventilation and extracorporeal membrane oxygenation, which increases treatment costs (6). The financial crisis caused by this virus causes mental problems and suicide among people (7). The complications caused by this virus include pulmonary, cardiovascular, neuropsychiatric,

hematologic, gastrointestinal, renal, endocrine, dermatologic, and musculoskeletal problems (8). However, the mechanism of the effects of factors causing long-term complications of COVID-19 is not yet clear.

There are several factors that affect COVID-19 incidence such as age, lung disease, hypertension, heart disease, kidney disease, or metabolic disorders. There are also other factors like physical distance, ventilation, face masks, socioeconomic factor, vaccination, SARS-CoV-2 variants, and the availability of COVID-19 testing that are helpful in this virus prediction (9). In critically ill patients with Covid-19, the body's metabolism may experience severe disturbances. For example, the function of pancreatic beta cells is often affected and the regulation of blood glucose is disturbed (10). Poor nutrition of critically ill patients may be associated with increased length of stay in the intensive care unit (ICU) and higher mortality (11). Due to the persistent pro-inflammatory immune response, the risk of nutritional stress such as malnutrition is higher in patients with COVID-19.

Previous studies reported that enteral feeding does not necessarily improve the status of COVID-19 patients (12). The results of one meta-analysis study indicated that early enteral nutrition is associated with a lower risk of mortality and SOFA (Sequential Organ Failure Assessment) score compared with delayed enteral nutrition in critically ill COVID-19 patients but it did not significantly (p >0.05) reduce the length of hospital stay, length of ICU stay and days on mechanical ventilation compared to delayed enteral nutrition or parenteral nutrition, respectively (13). Another meta-analysis showed that mortality was reduced in the early enteral nutrition group compared with the delayed enteral group. It has also been indicated that enteral nutrition may be the preferred route to enhance the integrity of the gut and promote immune function (14). The present study aimed to investigate the association of enteral feeding with biochemical and pathological indices associated with survival/mortality in COVID-19 patients.

Methods

Study Design and Participants

This case-control study was carried out from March 2021 to January 2022 on a total of 240 COVID-19 patients (120 patients eventually died after the study period and 120 patients were discharged) hospitalized in the ICU department of Razi hospital, Rasht, Iran. All patients required enteral nutrition according to the diagnosis of a specialist physician. Of these, some patients (n=121) as assessed by a dietitian, received the required nutritional support containing high protein, and high-volume formula following the latest medical guidelines. Also, 119 patients hospitalized in the ICU department of the same hospital received the standard formula.

Data Collection

General information on the patient's age, gender, height, weight, body mass index (BMI), length of stay in the ICU, APACH II, GCS, volume of formula received, presence of chronic diseases, and smoking were collected from the patient's medical record.

Statistical Analysis

To compare the demographic, anthropometric, biochemical, and pathological indices of the two groups by independent t-test and chi-square tests for quantitative and qualitative variables, respectively. The relationship between enteral nutrition and mortality was investigated using logistic regression. The confounding factors including age, gender, BMI, length of stay in the ICU, the Acute Physiology and Chronic Health Evaluation (APACHE II), the Glasgow Coma Scale (GCS), presence of chronic diseases, and smoking were adjusted in various regression models. SPSS 21 software was used for all statistical analyzes considering the significance level of P<0.05.

Results

The general characteristics of the COVID-19 patients included in this study are presented in Table 1. There was no significant difference between the two groups of patients (died versus recovered) for their

age (55.24±15.46 vs. 58.49±15.08 years), BMI (26.69±3.86 vs. 27.46±4.46 kg/m^2), and gender. However, the patient group that died had a significantly higher APACHII and lower GCS compared to the control group (both P<0.001). Also, the same group had significantly higher incidences of chronic disease and smoking compared to the control group (P<0.01).

The comparison of the volume and type of formula received among the case and control groups is presented in Table 2. The recovered patients received significantly more high protein (60.8% vs. 39.6%, P=0.004) and high volume (61.6% vs. vs. 42.3%, P=0.005) formula compared to the dead patients.

The association between mortality with the volume and type of formula is presented in Table 3. Mortality was inversely associated with high volume (OR:0.45 CI95%: 0.26-0.81, P=0.008) and high protein formula (OR:0.42 CI95%:0.23- 0.75, P=0.003). The results did not change after adjustments for age and sex (model 2), further adjustments for underlying diseases and smoking (Model 3), further adjustments for BMI (Model 4), and additional adjustments for APACHII (Model 5) (Figure 1).

Discussion

The present study investigated the association between enteral feeding and survival levels in COVID-19 patients admitted to the ICU. The group of patients who survived had lower smoking and incidences of chronic diseases compared with the group of patients who died during the experimental period. Our results indicated that the mortality was inversely associated with high volume and high protein formula, after adjustments for age and sex, underlying diseases, smoking, BMI, and APACHII.

Previous studies reported that there was a positive association between smoking and the mortality rate in CODIV-19 patients (15). As evident in this study and those reported in the past, critical COVID-19 patients may have a relatively high risk of sudden death due to the underlying comorbidities including cardiovascular disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and obstructive sleep apnea-hypopnea syndrome (OSAHS). Also, the underlying comorbidities were reported to be associated with higher in-hospital mortality (16) and lower survival rates (17).

The present study suggested an inverse relationship between mortality with high-volume and high-protein formula use in COVID-19 patients. In line with this study, Martindale et al. recommend using a standard high-protein ([?]20% protein) polymeric iso-osmotic enteral formula in the early acute phase of critical illness (18). Martindale et al reported that enteral nutrition (EN) should be initiated early after admission to the intensive care unit (ICU), while careful monitoring for gastrointestinal intolerance, hemodynamic instability, and metabolic derangements are essential (18, 19). In addition, a recent retrospective study has shown that early EN in paralyzed patients was associated with less hospital mortality, and there was no increase in ventilator-associated pneumonia (20). However, some studies reported contradictory results where no significant association between mortality and high protein formula was found (21). These results together strongly emphasize the importance of enteral feeding for survival levels in ICU patients with COVID-19. Hyperglycemia when occurring in a critical physiological state (22, 23) is likely to contribute to poor clinical outcomes (24). Insulin resistance and hyperglycemia result in muscle protein breakdown (25, 26). Hence, high-protein nutrition helps glucose control, reduces insulin requirements, improves muscle synthesis, and provides substrates needed at the sites of tissue injury in critically ill patients (27, 28). The positive effect of protein is also attributable to the maintenance of nitrogen balance and lean body mass (29) and its effect on the production of neurotransmitters, glutathione synthesis, and other compounds required during the acute infection phase (30).

Conclusion

The present study provides the first evidence for an association between enteral feeding with survival of ICU patients with COVID-19. According to the findings of the study, there was a significant inverse association between mortality and high-volume and high-protein formula. Prospective clinical trials and cohort studies should be performed to establish a causal relationship between enteral feeding and mortality and survival in ICU patients with COVID-19. If the results of the present study are confirmed in future research, it can be

considered an effective strategy to reduce the mortality rate of these patients by recommending high-calorie and high-protein formulas to patients admitted to the ICU.

Declarations:

Ethics approval and consent to participate

This study was approved by the Institutional Review Board at Shahid-Beheshti University of Medical Sciences (code: IR.SBMU.RETECH.REC.1398.783 (. All patients signed an informed consent form at baseline.

Consent for publication

Institutional consent forms were used in this study.

Availability of data and material

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Competing interests

The authors declare that they have no competing interests.

Funding

Funding for this study was provided by shahid beheshti University of Medical Sciences (74859).

Authors' contributions

SD, MGH, ZS, KHA, ZM, SHT, MM and FA designed the study, and were involved in the data collection, analysis, and drafting of the manuscript. BB, SD, SKH, MR, SGH, MP, and MGH were involved in the design of the study, analysis of the data, and critically reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We thank all the participants in this study for their good cooperation. This paper was taken from the approved research project of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

References

1. Baloch S, Baloch MA, Zheng T, Pei X. The coronavirus disease 2019 (COVID-19) pandemic. The Tohoku journal of experimental medicine. 2020;250(4):271-8.

2. Herby J, Jonung L, Hanke S. A literature review and meta-analysis of the effects of lockdowns on COVID-19 mortality. Studies in Applied Economics. 2022(200).

3. Lone SA AA. COVID-19 pandemic–an African perspective Emerging microbes & infections. 2020;9(1):1300-8.

4. JM C. Novel statistics predict the COVID-19 pandemic could terminate in 2022. Journal of Medical Virology. 2022;94(6):2845-8.

5. Takemoto ML MM, Andreucci CB, Knobel R, Sousa LA, Katz L, et al. Maternal mortality and COVID-19. The Journal of Maternal-Fetal & Neonatal Medicine. 2022;35(12):2355-61.

6. Jin H WH, Li X, Zheng W, Ye S, Zhang S, et al. Economic burden of COVID-19, China, January–March, 2020: a cost-of-illness study Bulletin of the World Health Organization. 2021;99(2):112.

7. Oberndorfer M DT, Brunnmayr M, Berger K, Dugandzic B, Bach M. Health-related and socio-economic burden of the COVID-19 pandemic in Vienna. Health & Social Care in the Community. 2022;30(4):1550-61.

8. Desai AD LM, Boursiquot BC, Wan EY. Long-term complications of COVID-19. American Journal of Physiology-Cell Physiology. 2022;322(1):C1-C11.

9. Shirley Gee Hoon Tang MHHH, Siti Rosilah Arsad, Pin Jern Ker, Santhi Ramanathan, Nayli Aliah Mohd Afandi, Madihah Mohd Afzal, Mei Wyin Yaw, Prajindra Sankar Krishnan, Chai Phing Chen, and Sieh Kiong TiongPaul B. Tchounwou, Academic Editor. Prerequisite for COVID-19 Prediction: A Review on Factors Affecting the Infection Rate. Int J Environ Res Public Health. 2022 Oct 11;19(20): 12997.

10. Kapoor R TL, Gupta N, Kaur H, Vidger AJ, Pollander AM, et al. Maintaining blood glucose levels in range (70–150 mg/dL) is difficult in COVID-19 compared to Non-COVID-19 ICU Patients—A retrospective analysis. Journal of Clinical Medicine. 2020;9(11):3635.

11. Neri SG TA, Gadelha AB, Lima RM. Body fat distribution in obesity and the association with falls: a cohort study of Brazilian women aged 60 years and over. . Maturitas. 2020;139:64-8.

12. Ojo O, Ojo OO, Feng Q, Boateng J, Wang X, Brooke J, et al. The effects of enteral nutrition in critically Ill patients with COVID-19: a systematic review and meta-analysis. Nutrients. 2022;14(5):1120.

13. Omorogieva Ojo OOO, Qianqian Feng, Joshua Boateng, Xiaohua Wang, Joanne Brooke, and Amanda Rodrigues Amorim Adegboye. The Effects of Enteral Nutrition in Critically Ill Patients with COVID-19: A Systematic Review and Meta-Analysis. Nutrients. 2022 Mar 7;14(5): 1120.

14. Feng Tian PTH, Matilde J Allingstrup, Gordon S Doig. Early Enteral Nutrition Provided Within 24 Hours of ICU Admission: A Meta-Analysis of Randomized Controlled Trials. Crit Care Med. 2018 Jul;46(7):1049-1056.

15. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dobbels F, Kirk R, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-eighth adult lung and heart-lung transplant report—2011. The Journal of Heart and Lung Transplantation. 2011;30(10):1104-22.

16. Wang YJ, Seggelke S, Hawkins RM, Gibbs J, Lindsay M, Hazlett I, et al. Impact of glucose management team on outcomes of hospitalizaron in patients with type 2 diabetes admitted to the medical service. Endocrine Practice. 2016;22(12):1401-5.

17. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18):1708-20.

18. Martindale R, Patel JJ, Taylor B, Arabi YM, Warren M, McClave SA. Nutrition therapy in critically ill patients with coronavirus disease 2019. Journal of parenteral and enteral nutrition. 2020;44(7):1174-84.

19. Thibault R, Seguin P, Tamion F, Pichard C, Singer P. Nutrition of the COVID-19 patient in the intensive care unit (ICU): a practical guidance. Critical Care. 2020;24(1):1-8.

20. Ohbe H, Jo T, Matsui H, Fushimi K, Yasunaga H. Early enteral nutrition in patients undergoing sustained neuromuscular blockade: a propensity-matched analysis using a nationwide inpatient database. Critical Care Medicine. 2019;47(8):1072-80.

21. Tao Q, Du J, Li X, Zeng J, Tan B, Xu J, et al. Network pharmacology and molecular docking analysis on molecular targets and mechanisms of Huashi Baidu formula in the treatment of COVID-19. Drug development and industrial pharmacy. 2020;46(8):1345-53.

22. Rice TW FD, Morris PE, et al. Dietary management of blood glucose in medical critically ill overweight and obese patients: an open label randomized trial. . JPEN J Parenter Enteral Nutr. 2019;43(4)471-480.2.

23. Rugeles SJ RJ, Diaz CE, Rosselli D. Hyperproteic hypocaloric enteral nutrition in the critically ill patient: a randomized controlled

clinical trial. . Indian J Crit Care Med. 2013;17(6):343-9.

24. Davidson P KC, Wien M. . Management of hyperglycemia and enteral nutrition in the hospitalized patient. Nutr Clin Pract. 2015;30(5):652-9.

25. Falciglia M FR, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with

admission diagnosis. Crit Care Med. 2009;37(12):3001-9.

26. Mesotten D PJ, Kosiborod M. Glucose management in critically ill adults and children. . Lancet Diabetes Endocrinol. 2015;3(9):723-33.

27. Phillips SM DR, Moore FA, Paddon-Jones D, Weijs PJ. Protein turnover and metabolism in the elderly intensive care unit patient. Nutr Clin Pract. 2017;32(1_suppl):112S-20S.

28. LJ H. High-protein hypocaloric nutrition for non-obese critically ill patients.. ;:. Nutr Clin Pract. 2018;33(3)(325-332).

29. Weijs PJ SS, 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. J Parenter Enteral Nutr.

30. Furst P SP. What are the essential elements needed for the determination of amino acid requirements in humans? J Nutr 2004;134:1558Se65S.

Table 1. Characteristics of the COVID-19 participants recovered and died after hospitalization ICU

Parameters	**Controls (Recovered) n=120**	**Cases (dead) n=120**	*P*-**value**
Age (y)	55.24±15.46	58.49±15.08	0.139
Gender	*Gender*	*Gender*	
Male	61 (50.7%)	58 (48%)	0.770
Female	59 (49.3%)	62 (53%)	0.770
BMI (kg/m^2)	26.69±3.86	27.46±4.46	0.180
Length of stay in ICU(d)	4.43±1.37	4.57±1.85	0.500
APACH II	30.17 ±5.52	32.9 ±4.09	<0.001

GCS	9.60±1.84	7.91±0.83	<0.001
Volume of formula received (ml/d)	632.88±214.34	425.04±24.93	0.173
Presence of chronic diseases	18(24.0%)	66(44.6%)	0.003
Smokers	4(5.5%)	31(21.1%)	0.003

APACHE: Acute Physiology and Chronic Health Evaluation; BMI: body mass index; GCS: Glasgow coma scale.

Table 2. The comparison of the volume and type of formula received among the case and control groups

	Controls (Recovered) n=120	**Cases (dead) n=120**	*P*-**value**
Formula Type	Formula Type	Formula Type	Formula Type
Standard	47 (39.2%)	72 (60.4%)	0.004
High protein	73 (60.8%)	48 (39.6%)	
Formula volume	Formula volume	Formula volume	Formula volume
<600 ml/d	46 (38.4%)	69 (57.7%)	0.005?¿?
600 ml/d	74 (61.6%)	51 (42.3%)	

Table 3. The association between mortality with the volume and type of formula

	High volume ([?]600ml/d)	**High volume ([?]600ml/d)**	**High protein**	**High protein**
	OR (CI95%)	**P**	**OR (CI95%)**	**P**
Model 1	0.45 (0.26-0.81)	0.008	0.42(.23- .75)	0.003
Model 2	0.42 (0.23-0.76)	0.004	.41(.23-0.74)	0.003
Model 3	0.44 (0.24-0.82)	0.010	0.43 (0.23-0.79)	0.007
Model 4	.445 (.24- .82)	0.010	.43(0.23-0.80)	0.008
Model 5	0.52 (0.27-0.97)	0.043	0.44 (0.23-0.84)	0.013

Model 1: Crude, Model 2: adjusted for age and sex, Model 3: further adjustment for underlying diseases and smoking, Model 4: further adjustment for BMI, Model 5: further adjustment for APACHII

Figure 1. The effects of high-protein and high-volume formula on mortality in patients with COVID-19