ORIGINAL ARTICLE

# Early Enteral Nutrition and Clinical Outcomes in COPD Patients Requiring Mechanical Ventilation

**Fariba Mansouri[1], Majid Akrami[2], Neda Faraji[3], Masoomeh Nataj Majd[4]**

*[1] Department of Respiratory, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran*
*[2] Department of Anesthesiology, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran*
*[3] Department of Internal Medicine, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran*
*[4] Department of Anesthesiology, Arash Hospital, Tehran University of Medical Sciences, Tehran, Iran*

***Received: 24 Apr. 2023; Accepted: 14 Aug. 2023***

**Abstract**- Early commencement of enteral nutrition (EEN) in critically ill patients requiring mechanical ventilation may improve outcomes. But there is a lack of enough data regarding EEN effects on COPD exacerbation patients' outcomes. This retrospective study involved 129 COPD exacerbation patients who received invasive mechanical ventilation in ICU. The clinical outcomes were compared based on the timing of enteral nutrition (<48h vs >48h) during 60 days of ICU stay. We surveyed and analyzed mortality, pleural effusion, ventilator-associated pneumonia, weaning failure, cardiac arrhythmias, GI bleeding, electrolyte imbalances, renal dysfunction and length of ICU stay. All analyses were performed using SPSS software version 22.0. 129 COPD-exacerbated patients (EEN group n=66; DEN group n=63) who met the inclusion criteria were enrolled in the study. EEN group had a lower death rate (39% vs 44.4%) than the DEN group, but no significant difference was found in the overall mortality during the 60-day follow-up (*P* 0.561). The EEN group also had lower ICU stay and pleural effusion rate than the DEN group (*P*:0.006 and 0.020 respectively). No significant differences were found in other outcomes. Early enteral nutrition might be associated with shorter ICU stay and lower odd ratio of acquisition of pleural effusion in COPD patients requiring invasive mechanical ventilation. EEN could not decrease mortality rate compared with DEN in the current study.

*Acta Med Iran* 2023;61(9):547-554.

**Keywords:** Nutrition; Chronic obstructive pulmonary disease enteral feeding; Critical illness; Patient outcome

## Introduction

Nutritional support plays a pivotal role in the clinical management of critically ill patients under mechanical ventilation (1,2). Based on the latest international guidelines, enteral nutrition is being preferred over parenteral nutrition and should be initiated as early as possible in patients requiring invasive mechanical ventilation (2-4). The starting of enteral nutrition within 48 hours after endotracheal intubation and mechanical ventilation may improve outcomes in critically ill patients (5-7). Early enteral nutrition (EEN) within 24 to 48 hours of ICU admission can preserve gastrointestinal mucosa integrity, enhance immune responses and diminish nosocomial infection possibilities (2); also, increased immunoglobulin A production that produces protection versus airway infections (8). A meta-analysis, by Tian. F in 2018, showed that EEN reduced mortality rate and pneumonia when compared with delayed enteral nutrition (DEN) in ICU patients; they revealed that there was an association between the onset of malnutrition and decreased immune function that developed nosocomial infections, impaired respiratory function and increased risk of death in critical illnesses (9).

Chronic obstructive pulmonary disease (COPD) is a progressive multi-organ systemic chronic disease, in which the patient's protein requirement increases (1,10-12). On the other hand, nutritional depletion in COPD is

**Corresponding Author:** M. Akrami
Department of Anesthesiology, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 9123270714, E-mail address: majakrami@sina.tums.ac.ir

a complex issue that can lead to imbalances of energy, protein, and periods of inflammation. This can result in weight loss, sarcopenia, and pulmonary cachexia (10). In fact, the etiology of malnutrition in COPD is very complex and multi-factorial and the rate of mortality can increase more in the presence of malnutrition in critically ill patients requiring admission to ICU (8).

COPD patients during acute exacerbation need both respiratory and nutritional support in the intensive care unit, and poor body weight and less fat free mass recognized as poor prognostic factors (13-15). Indeed, increased action of breathing, hypermetabolism, hypoxemia and systemic inflammation play a key role in developing cachexia and deteriorating clinical outcomes in COPD patients admitted to ICU (1). Insufficient nutritional supply results in increased susceptibility to infections, weight loss and reduction in muscle mass and imbalances of energy; therefore, it may have undesirable impact on patients' outcomes and mortality especially in COPD patients who have marginal ventilatory reserve (1,8,16). Shruti K *et al.*, mentioned that the reported mortality rate related to COPD exacerbation was ranging from 11% to 32%. It is much higher in several research reports on COPD cases requiring invasive mechanical ventilation for their acute exacerbation (17). Padilla conducted a systematic review and showed that uncertainty regarding early enteral nutrition, compared with delayed enteral nutrition, affects the risk of mortality within 30 days (18). Additionally, Moon *et al*., reported that the optimal timing of enteral nutrition in sepsis patients is controversial among societal guidelines (19).

Given that, there is a lack of enough data upon EEN effects on COPD exacerbation outcomes, and also because of the controversy against the relation between the early commencement of enteral nutrition and mortality rate in critically ill patients, the current study was designed retrospectively to answer the question whether EEN could effect on mortality rate and other outcomes in COPD patients with exacerbation requiring IMV.

## Materials and Methods

### Participants and study design

This study has been approved by the ethics committee of Tehran University of Medical Sciences (Approval number: 1400-1-101-51620). The current retrospective observational study was conducted at the Baharloo Hospital, a general teaching hospital, from January 2017 to May 2023. All information from patients' profiles was collected confidentially and used only for this study. Patient information was not reported individually, and all information was reported in groups. The patient's legal guardian was properly informed about the study, and informed consent was obtained. Adult patients with COPD exacerbation who were admitted to ICU and supported by invasive mechanical ventilation were retrospectively analyzed. Patients were divided into two groups according to the initiation time of enteral nutrition. Nutritional support was started within the first 48 hours of admission at ICU in early enteral nutrition (EEN) group. The initiation of nutritional support after 48 hours was defined as delayed enteral nutrition (DEN); the crystalloid fluid was administered to compensate for DEN group's fluid requirement in the first 48 h of ICU admission. The enrolled patients were followed during 60 days to investigate the effect of EEN on the mortality and other outcomes of COPD patients. Demographic data, the rate of pleural effusion, ventilator associated pneumonia (VAP), weaning failure from mechanical ventilator, electrolyte imbalances, GI bleeding, cardiac arrhythmias and length of ICU stay were retrospectively analyzed. The study was retrospective, and data gathered from written medical records; therefore, the patient's selection was not conducted blindly.

### Subject and exclusion criteria

The smoker or ex-smoker patients who were diagnosed and previously treated by an internist as COPD patients and needed ICU respiratory care with invasive mechanical ventilation were selected. The age of enrolled patients was between 40 and 80 years old. Those patients who had uremia, GFR less than 50 mL/min/ 1.73 $m^2$ (20), heart failure, liver dysfunction, or diabetes mellitus were excluded. Also, those who experienced septic shock or needed high doses of inotropic drugs were excluded from the study. Moreover, the patients who experienced GIB within the first 72 hours of admission and were deprived of enteral nutrition were removed from the study.

### Definition

Early enteral nutrition (EEN) was defined as a standard formula started within 48 hours of ICU admission; the initiation of enteral nutritional support after 48 hours was considered as delayed enteral nutrition (DEN). The hospital-approved formula was delivered via a 14-16 French gastric tube. Patients with enteral intolerance during the study period were excluded (21).

Chronic obstructive pulmonary disease (COPD) was described by irreversible airflow obstruction and advanced reduction of lung function based on the Global Initiative for Obstructive Lung Disease (GOLD) and the

European Respiratory Society (ERS) (22).

Weaning failure from mechanical ventilation was characterized by the failure of spontaneous breathing trial (SBT) or the need for re-intubation within 48 h following endotracheal extubation (23).

Pleural effusion was diagnosed by an internist through medical examination and chest x-ray. Then, the radiography and ultrasonography findings were double checked by radiologist. If the amount of pleural fluid was more than 200 ml, the finding was considered as pleural effusion (24).

Ventilator associated pneumonia (VAP) was specified as a lower respiratory tract infection taking place after at least 48 hours of endotracheal intubation (25). VAP was confirmed by bacteriological results from a distal respiratory specimen in each suspected patient. Broncho-alveolar lavage or tracheobronchial aspiration were used in this regard (2).

The normal range of serum sodium ($NA^+$) and potassium ($K^+$) concentration were defined as 135-145 mEq/L and 3.5-5 mEq/L respectively. The normal range of calcium ($Ca^{++}$) was specified as 8.2 mg/dl-10.4 mg/dl, and for magnesium ($Mg^{++}$) it was 1.9-2.7 mg/dl. Electrolyte imbalances were specified as the serum electrolyte levels were outside the normal range.

A decrease in Glomerular filtration rate (GFR) of more than 50% of its base line was determined as impaired renal function.

Nasogastric tube secretions of more than 50 ml containing bright red blood or dark brown resembling coffee grounds in texture was considered as upper GI bleeding; black or tarry stool was defined as lower GI bleeding. Every event of upper or lower gastrointestinal bleeding (GIB) was recorded.

**Outcomes**

The primary outcome of interest was mortality. ICU length of stay, VAP, pleural effusion, weaning failure, cardiac arrhythmias, GIB, electrolyte imbalances and impaired renal function were evaluated as secondary outcomes.

**Data collection**

Relevant data were retrospectively collected through patients' medical record sheets. This data included demographic characteristics, length of ICU stays, laboratory findings, pleural effusion, cardiac arrhythmias, GI bleeding, mechanical ventilation weaning failure, ventilator-associated pneumonia, information concerning the underlying diseases and mortality, as a primary outcome, within 60 days.

**Statistical analysis**

The mean±standard deviation or frequency (percent) were used for numeric and categorical variables, respectively. The student's independent test was used to compare two continuous variables and chi-square test was applied to examine differences between two categorical variables. The association between feeding and the pleural effusion was assessed using a logistics regression model adjusted for VAP and GFR as confounders. All data analyses were performed with Stata software, and a *P* of less than 0.05 was considered significant.

## Results

A total of 158 medical records concerning critically ill COPD patients who needed invasive mechanical ventilation were entered in this study and retrospectively analyzed. Because of missing or incomplete data in patients' record sheets, and also because of failure to follow-up for several cases, 29 patients were removed from the survey. Finally, 129 patients entered the study; 66 cases were registered in the early enteral nutrition group (<48 h), and 63 patients entered in the delayed enteral nutrition group.

All variables, characteristics of patients and outcomes, are summarized in Table 1. The mean age of the EEN group was 70.09±8.54 years and for the DEN group, it was 69.95±8.82 years. Of the 66 patients in the EEN group, 55 cases (83.3%) were male, and in the DEN group 54 patients (85.7%) were male participants. The mean of BMI was 25.68±4.52 and 26.02±4.68 in EEN and DEN group, respectively. Differences in age, sex and BMI were not statistically significant between the two groups.

The ICU length of stay was statistically different between the two groups. The mean days of ICU length of stay was 15.85±11.91 and 22.17±13.87 for EEN and DEN group, respectively. (*P*:0.006) Of 129 total patient population, 54 cases (41.9%) died. The rate of death was lower in the EEN group compared with the DEN group (39.4% vs 44.4%), but no significant difference was found in the overall mortality for 60 day- follow up between two groups. (*P*:0.561) The rate of pleural effusion in DEN group (63.5 %) was significantly higher than EEN group (43.9%). (*P*:0.020) Except for the pleural effusion and ICU length of stay, there were no significant differences in other outcomes including VAP, weaning failure, cardiac arrhythmias, GIB, electrolyte imbalances and renal dysfunction among study participants (*P*:>0.05) (Table 1).

Furthermore, in the current study, of 129 total study population, 69 patients developed pleural effusion (PE) and 60 cases did not experience PE problem. Therefore, several important variables were compared between COPD patients who developed pleural effusion (PE) and cases without PE during the study period. No significant differences were found between the two groups comparing age, BMI and gender. (*P*:0.926, 0.839 and 0.525 respectively). However, VAP rate and renal dysfunction frequency were significantly higher in cases with pleural effusion than the other participants without pleural effusion. VAP was reported in 17 cases (24.6%) and 7 patients (11.7%) in PE group and cases without PE respectively (*P*:0.059, borderline significant). Renal dysfunction was diagnosed in 17 PE cases (24.6%) compared to 4 patients (6.7%) in group without PE (*P*:0.006). Moreover, the rate of PE was significantly lower in the early enteral nutrition (EEN) cases, 42%, compared to delayed enteral nutrition (DEN), 58 % (*P*:0.026) (Table 2).

Pleural effusion odd ratio between EEN and DEN group has demonstrated in Table 3. After adjusting the confounding variables, the odd ratio for acquisition of pleural effusion was compared between EEN and DEN group. The odd of pleural effusion occurrence in DEN cases was 2.34 times more than EEN patients. (CI: 95% and *P*:0.023).

**Table 1. Characteristics and outcomes in COPD exacerbation patients requiring invasive mechanical ventilation**

| Variables | | Total (n=129) | Enteral nutrition after ICU admission | | *P* |
|---|---|---|---|---|---|
| | | | EEN (n=66)<48 h | DEN (n=63) >48h | |
| Age, year (Mean±SD) | | 70.02 ± 8.65 | 70.09 ± 8.54 | 69.95 ± 8.82 | 0.928 |
| Gender n (%) | Male | 109 (84.5) | 55 (83.3) | 54 (85.7) | 0.709 |
| | Female | 20 (15.5) | 11 (16.7) | 9 (14.3) | |
| BMI, Kg/M$^2$ (Mean±SD) | | 25.84 ± 4.59 | 25.68 ± 4.52 | 26.02 ± 4.68 | 0.681 |
| ICU LOS*, day (Mean±SD) | | 18.94±13.4 | 15.85 ± 11.91 | 22.17 ± 13.87 | 0.006 |
| Mortality n (%) | Death | 54 (41.9) | 26 (39.4) | 28 (44.4) | 0.561 |
| | Alive | 75 (58.1) | 40 (60.6) | 35 (55.6) | |
| VAP* n (%) | | 24 (18.6) | 12 (18.2) | 12 (19) | 0.899 |
| Pleural effusion n (%) | | 69 (53.5) | 29 (43.9) | 40 (63.5) | 0.020 |
| Weaning failure n (%) | | 34 (26.4) | 15 (22.7) | 19 (30.2) | 0.338 |
| Cardiac arrhythmias n (%) | | 39 (30.2) | 18 (27.3) | 21 (33.3) | 0.454 |
| GIB* n (%) | | 11 (8.5) | 5 (7.6) | 6 (9.7) | 0.711 |
| GFR* < 50% n (%) | | 21 (16.3) | 11 (16.7) | 10 (15.9) | 0.936 |
| Electrolyte imbalances**n (%) | Na+ | 35(27.3) | 16(24.2) | 19(30.6) | 0.417 |
| | K+ | 38(29.5) | 17(25.8) | 21(33.3) | 0.374 |
| | Ca++ | 19(14.7) | 10(15.2) | 9(14.3) | 0.861 |
| | Mg++ | 23(17.8) | 11(16.7) | 12(19) | 0.754 |

*Data are expressed as mean ± standard deviation or frequency (percent)
ICU: intensive care unit, LOS: length of stay; BMI: body mass index; VAP: ventilator-associated pneumonia; GFR: glomerular filtration rate; GIB: gastrointestinal bleeding
** Electrolyte imbalances: values under or upper than normal range

**Table 2. Clinical variables between COPD patients who experiencing pleural effusion compared to patients without pleural effusion**

| Variables | | With Pleural effusion (PE+) (n=69) | Without Pleural effusion (PE-) (n=60) | *P* |
|---|---|---|---|---|
| | | Frequency (percent) | Frequency (percent) | *P* |
| Age, year (Mean±SD) | | 69.96±8.41 | 70.10 ±8.98 | 0.926 |
| BMI, Kg/M$^2$ (Mean±SD) | | 25.77±4.48 | 25.93±4.74 | 0.839 |
| Gender | Male n (%) | 57 (82.6) | 52 (86.7) | 0.525 |
| | Female n (%) | 12 (17.4) | 8 (13.3) | |
| VAP | With VAP n (%) | 17 (24.6) | 7 (11.7) | 0.059 |
| | Without VAP n (%) | 52 (75.4) | 53 (88.3) | |

**Cont. table 2.**

| | | | | |
|---|---|---|---|---|
| **GFR** | **Impaired GFR n (%)** | 17 (24.6) | 4 (6.7) | 0.006 |
| | **Normal GFR n (%)** | 52 (75.4) | 56 (93.3) | |
| **Feeding status** | **Early feeding n (%)** | 29 (42) | 37 (61.7) | 0.026 |
| | **Late feeding n (%)** | 40 (58) | 23 (38.3) | |

*Data are expressed as mean±standard deviation or frequency (percent) BMI: body mass index; VAP: ventilator associated pneumonia; GFR: glomerular filtration rate

**Table 3. Comparing pleural effusion odd ratio between EEN and DEN group**

| Enteral nutrition | Crude odd ratio (95% CI) | *P* | Adjusted odds ratio * (95% CI) | *P* |
|---|---|---|---|---|
| **Early feeding** | 1 | 0.027 | 1 | 0.023 |
| **Late feeding** | 2.21 (1.09-4.48) | | 2.34 (1.12-4.91) | |

CI: confidence interval
*Adjusted for AGE, SEX, ↓GFR≥50% of its baseline, and VAP
VAP: ventilator-associated pneumonia
GFR: glomerular filtration rate

## Discussion

In the present study, administration of early enteral nutrition (EEN) within the first 48 h of ICU admission reduced the ICU length of stay in critically ill COPD patients; however, it had no impact on mortality reduction and VAP rate in the study population. Moreover, the EEN group developed a lower rate of pleural effusion (PE) compared with DEN group. In a similar way, X. Zheng *et al*., stated that no significant difference was found in the risk of mortality regarding initiation of EEN within 48 h comparing DEN for critically ill patients (26). Consistent with our results, Zheng also revealed that early EEN reduced the duration of mechanical ventilation and lengths of hospital stay, but it has no distinct effect on mortality in the patients with sepsis under mechanical ventilation (20). In another study, F. Tian *et al*., stressed that there was no difference in mortality between EEN and all other forms of nutrition support in critically ill patient populations. They identified 16 RCTs that compared EEN commenced within the first 24 hours of ICU admission with DEN or other types of nutritional support. They concluded that risk of developing pneumonia decreased after the beginning of EEN, but the authors failed to find a statistically significant difference regarding ICU length of stay or duration of invasive mechanical ventilation (IMV) between groups (9).

On the other hand, G. Doig *et al*., demonstrated that there was a statistically significant reduction in mortality and pneumonia attributable to early initiation of enteral nutrition during ICU admission. However, they argued about the small trial size and low trial quality of studies in their systematic review, and they suggested that the findings of this meta-analysis should be confirmed by large scale multi-center studies (6). Also, Peng-Fei Li and associates presented that even in traumatically ill patients, EEN could reduce mortality rate and hospital length of stay (27). Contrary to their findings, our single-center study found no significant differences regarding mortality rate and ventilator associated pneumonia.

Nevertheless, pleural effusion was significantly higher in DEN group compared with EEN cases. (*P*:0.02) In fact, in our study, the adjusted odd ratio for acquisition of pleural effusion in DEN group was 2.34 times more than EEN patients. The Crude OR, which was adjusted for low GFR, VAP, sex, and age, helps to understand how adjusting for these variables impacts the effect of the nutrition variable on pleural effusion. (CI: 95%; *P*:0.023, and adjusted for AGE, SEX, GFR and VAP). Pleural effusions in critically ill patients can be attributed to several factors, including heart failure, pneumonia, hypoalbuminemia, and fluid overload (28). In our study, the DEN group was administered pure crystalloid fluid for the initial 48 hours. It is plausible that the increased fluid intake in the DEN group elevated the hydrostatic pressure, thereby potentially contributing to a higher prevalence of pleural effusion. Consequently, acquisition of pleural effusion in patients under mechanical ventilation adversely affected the weaning process resulting in increased duration of mechanical ventilation and lengths of hospital stay. In the same way, Razazi *et al*., demonstrated, in a prospective observational multicenter study, that pleural effusion was found in one third of ICU cases at the initiation of weaning process and had a negative impact on liberation time from mechanical ventilation (29). Likewise, Maslove *et al*., explained that pleural effusion in ICU cases is commonly caused by volume overload, reduced plasma oncotic pressure, changes in pleural pressure frequently attributable to mechanical ventilation or it might be a consequence of pleural infection, pulmonary thrombus embolism or carcinoma (30). A cohort study about the role of Hematocrit Concentration on Successful Extubation in Critically Ill Patients in the Intensive Care Units revealed that improved management of underlying conditions and reducing the duration of mechanical ventilation may ensure successful extubation more reliably than addressing anemia alone. This aspect warrants particular attention, particularly among female patients (31).

There are several pathways in which nutrition can affect pleural effusion. For instance, certain nutritional deficiencies or excesses might affect systemic inflammation and capillary permeability, potentially leading to an increased exudation of fluid, protein, cells, and other serum constituents into the pleural space. The vitamin D deficiency has been associated with infectious and noninfectious pleural effusions (32). Also, disease-related malnutrition can also affect pleural effusion (33). Although we have explained the likely mechanism of PE in DEN group, there are several important limitations in our study that must be acknowledged.

## Limitations

This study has several limitations. First, the oncotic pressure of plasma was not measured and there were no data available regarding blood level of albumin or total serum protein in patients' medical profiles. Second, the APACHE II score was not calculated due to insufficient data on the medical record sheet. Third, we encountered a lack of data regarding the nutritional status of the patient population prior to hospitalization; making it infeasible to compare illness severity between study groups. Fourth, the small study group and the lack of a control group might effect on the generalizability of the results. Finally, single-center retrospective study design should also be considered as another limitation. Therefore, further exploration of the validity of our findings is needed through prospective multi-center studies with a larger sample.

Early enteral nutrition (EEN) within the first 48 h of ICU admission is associated with shorter ICU stay, and it also decreases the odd ratio of acquisition of pleural effusion in COPD patients requiring invasive mechanical ventilation. Although EEN could not lower mortality rate in critically ill COPD patients compared with DEN, it may contribute to improved outcomes in COPD patients by reducing complications and length of stay in the ICU and hospital.

## Acknowledgements

Thanks to the nurses at Baharloo Hospital who enthusiastically contributed to COPD project.

## References

1. DeBellis HF, Fetterman Jr JW. Enteral nutrition in the chronic obstructive pulmonary disease (COPD) patient. J Pharm Pract 2012;25:583-5.
2. Brisard L, Le Gouge A, Lascarrou JB, Dupont H, Asfar P, Sirodot M, et al. Impact of early enteral versus parenteral nutrition on mortality in patients requiring mechanical ventilation and catecholamines: study protocol for a randomized controlled trial (NUTRIREA-2). Trials 2014;15:507.
3. Preiser JC, Arabi YM, Berger MM, Casaer M, McClave S, Montejo-González JC, et al. A guide to enteral nutrition in intensive care units: 10 expert tips for the daily practice. Crit Care 2021;25:424.
4. Mehta Y, Sunavala JD, Zirpe K, Tyagi N, Garg S, Sinha S, et al. Practice Guidelines for Nutrition in Critically Ill Patients: A Relook for Indian Scenario. Indian J Crit Care Med 2018;22:263-73.
5. Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest 2006;129:960-7.
6. Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. Intensive Care Med 2009;35:2018-27.
7. Sierra-Colomina M, Yehia NA, Mahmood F, Parshuram C, Mtaweh H. A Retrospective Study of Complications of Enteral Feeding in Critically Ill Children on Noninvasive Ventilation. Nutrients 2023;15:2817.
8. Lewis SR, Schofield- Robinson OJ, Alderson P, Smith AF. Enteral versus parenteral nutrition and enteral versus a

combination of enteral and parenteral nutrition for adults in the intensive care unit. Cochrane Database Syst Rev 2018;6:CD012276.
9. Tian F, Heighes PT, Allingstrup MJ, Doig GS. Early Enteral Nutrition Provided Within 24 Hours of ICU Admission: A Meta-Analysis of Randomized Controlled Trials. Crit Care Med 2018;46:1049-56.
10. Collins PF, Yang IA, Chang YC, Vaughan A. Nutritional support in chronic obstructive pulmonary disease (COPD): an evidence update. J Thorac Dis 2019;11:S2230-S7.
11. Nan Y, Zhou Y, Dai Z, Yan T, Zhong P, Zhang F, et al. Role of nutrition in patients with coexisting chronic obstructive pulmonary disease and sarcopenia. Front Nutr 2023;10:1214684.
12. Bernardes S, Eckert IDC, Burgel CF, Teixeira PJZ, Silva FM. Increased energy and/or protein intake improves anthropometry and muscle strength in chronic obstructive pulmonary disease patients: a systematic review with meta-analysis on randomised controlled clinical trials. Br J Nutr 2023;129:1332-49.
13. Brown H, Dodic S, Goh SS, Green C, Wang WC, Kaul S, et al. Factors associated with hospital mortality in critically ill patients with exacerbation of COPD. Int J Chron Obstruct Pulmon Dis 2018;13:2361-6.
14. Collins PF, Elia M, Stratton RJ. Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respirology 2013;18:616-29.
15. Hegazi RA, Wischmeyer PE. Clinical review: Optimizing enteral nutrition for critically ill patients--a simple data-driven formula. Crit Care 2011;15:234.
16. Yazdanpanah L, Shidfar F, Moosavi AJ, Heidarnazhad H, Haghani H. Energy and protein intake and its relationship with pulmonary function in chronic obstructive pulmonary disease (COPD) patients. Acta Med Iran 2010:374-9.
17. Gadre SK, Duggal A, Mireles-Cabodevila E, Krishnan S, Wang XF, Zell K, et al. Acute respiratory failure requiring mechanical ventilation in severe chronic obstructive pulmonary disease (COPD). Medicine (Baltimore) 2018;97:e0487.
18. Padilla PF, Martínez G, Vernooij RW, Urrútia G, Figuls MRI, Cosp XB. Early enteral nutrition (Within 48 hours) versus delayed enteral nutrition (after 48 hours) with or without supplemental parenteral nutrition in critically ill adults. Cochrane Database Syst Rev 2019;2019:CD012340.
19. Moon SJ, Ko RE, Park CM, Suh GY, Hwang J, Chung CR. The Effectiveness of Early Enteral Nutrition on Clinical Outcomes in Critically Ill Sepsis Patients: A Systematic Review. Nutrients 2023;15:3201.
20. Delanaye P, Schaeffner E, Ebert N, Cavalier E, Mariat C, Krzesinski JM, et al. Normal reference values for glomerular filtration rate: what do we really know? Nephrol Dial Transplant 2012;27:2664-72.
21. Fuentes Padilla P, Martínez G, Vernooij RW, Urrútia G, Roqué IFM, Bonfill Cosp X. Early enteral nutrition (within 48 hours) versus delayed enteral nutrition (after 48 hours) with or without supplemental parenteral nutrition in critically ill adults. Cochrane Database Syst Rev. 2019;2019:CD012340.
22. Akkermans RP, Biermans M, Robberts B, ter Riet G, Jacobs A, van Weel C, et al. COPD prognosis in relation to diagnostic criteria for airflow obstruction in smokers. Eur Respir J 2014;43:54-63.
23. Boles J-M, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. Eur Respir J 2007;29:1033-56.
24. Karkhanis VS, Joshi JM. Pleural effusion: diagnosis, treatment, and management. Open Access Emerg Med 2012;4:31-52.
25. Mohammadreza S, Sirous J, Lida G, Hossein Malekafzali A, Alireza A, Mohammad Taghi B, et al. Ventilator-associated Pneumonia: Multidrug Resistant Acinetobacter vs. Extended Spectrum Beta Lactamase-producing Klebsiella. J Infect Dev Ctries 2020;14:660-3.
26. Zheng XX, Jiang LX, Huang M. Early versus delayed enteral nutrition in critically ill patients: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2019;12:4755-63.
27. Li PF, Wang YL, Fang YL, Nan L, Zhou J, Zhang D. Effect of early enteral nutrition on outcomes of trauma patients requiring intensive care. Chin J Traumatol 2020;23:163-7.
28. Bediwy AS, Al-Biltagi M, Saeed NK, Bediwy HA, Elbeltagi R. Pleural effusion in critically ill patients and intensive care setting. World J Clin Cases 2023;11:989-99.
29. Razazi K, Boissier F, Neuville M, Jochmans S, Tchir M, May F, et al. Pleural effusion during weaning from mechanical ventilation: a prospective observational multicenter study. Ann Intensive Care 2018;8:103.
30. Maslove DM, Chen BT, Wang H, Kuschner WG. The diagnosis and management of pleural effusions in the ICU. J Intensive Care Med 2013;28:24-36.
31. Beigmohammadi MT, Khan ZH, Samadi S, Mahmoodpoor A, Fotouhi A, Rahimiforoushani A, et al. Role of hematocrit concentration on successful extubation in critically ill patients in the intensive care units. Anesth Pain Med 2016;6:e32904.
32. Amado CA, García-Unzueta MT, Fariñas MC, Santos F, Ortiz M, Muñoz-Cacho P, et al. Vitamin D nutritional status and vitamin D regulated antimicrobial peptides in serum and pleural fluid of patients with infectious and noninfectious pleural effusions. BMC Pulm Med

2016;16:99.

33. Dehesa-López E, Martínez-Felix JI, Inzunza-Soto MY, Sánchez-Ochoa JÁ, de los Angeles Espinoza-Cuevas M, Valdez-Ortiz R. Clinical impact of disease-related malnutrition and fluid overload assessment via bioimpedance vector analysis in hospitalized patients. Clin Nutr ESPEN 2020;39:131-6.