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Comparison of nutritional adequacy in adult patients with acute respiratory distress syndrome with and without veno-venous extracorporeal membrane oxygenation: a single-center experience

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ABSTRACT

Objectives: Limited data is available regarding nutrition practices for patients with acute respiratory distress syndrome (ARDS) who are also receiving veno-venous-extracorporeal membrane oxygenation (VV-ECMO). The aim of the study was to describe the nutritional status of patients receiving VV-ECMO and compared with those who did not.

Methods: Patients (> 18 years-old) diagnosed with ARDS who received VV-ECMO (≥ 72 hours) were included in this retrospective study. The daily achievement of an energy target (%) and average protein intake during 2 weeks after initiation of VV-ECMO were calculated. Adequate feeding was defined as achieving 80-110% of the calculated target. The duration before initiating parenteral (PN) and enteral nutrition (EN), feeding route, length of intensive care, and hospital stay were evaluated. Data was compared between groups.

Results: In this study, 24 patients were included, of whom 12 received VV-ECMO. EN was started in a median 1.5 and 1 day in the VV-ECMO and non-ECMO groups, respectively. In the VV-ECMO group, 75% of the patients could achieve nutritional adequacy (> 80% energy goal) and 83.3% in the non-ECMO group ($p = 0.615$). PN being required in 4 (33.3%) patients who received VV-ECMO and 3 (25%) patients who did not ($p = 0254$). Ten of all patients experienced inadequate EN because of hemodynamic instability (n = 3), prone position (n = 4), gastric distension (n = 2) and diarrhea (n = 1).

Conclusions: VV-ECMO was not an obstacle for adequate nutrition, but prone position and hemodynamic instability were common causes of enteral feeding interruptions and inadequate energy delivery.

Keywords: Acute respiratory distress syndrome, veno-venous-extracorporeal membrane oxygenation, nutrition, enteral, parenteral, critically ill

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by poor oxygenation and non-compliant lungs. This disorder is associated with capillary endothelial injury and diffuse alveolar damage [1]. For treating ARDS, extracorporeal membrane oxygenation (ECMO) may be required as well as ventilation with low tidal volume, prone position, and high positive end expiratory pres-

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sure (PEEP) applications. ECMO may be a promising method for treating ARDS in the future [2]. Although the main treatment strategies for ARDS are respiratory support and treatment of the underlying disease, supportive care is necessary. The pro-inflammatory response and related hypercatabolism in ARDS can cause significant nutritional deficiency, and nutritional support should not be ignored in critically ill patients with ARDS [3].

Mechanically ventilated patients are at a high risk of malnutrition, and malnutrition can cause respiratory muscle weakness, prolonged mechanical ventilation (MV), and length of stay (LOS) in intensive care unit (ICU) [4, 5]. In addition to MV administration, patients who need venovenous ECMO (VV-ECMO) are the most severely ill patients with prolonged ICU-LOS and increased nutritional support [6]. Full calorie and protein nutritional support is essentially recommended by Extracorporeal Life Support Organization (ELSO) for patients undergoing ECMO [7]. In the absence of detailed guidelines on nutrition for ECMO patients from ELSO, healthcare professionals may have adopted different approaches and practices based on their individual judgement, experience, and the availability of evidence from other sources [3, 8].

Despite the concerns that ECMO administration will cause gut barrier dysfunction and allow bacterial translocation, studies suggest that enteral nutrition (EN) is well tolerated in patients undergoing ECMO. Additionally, reporting of EN related adverse events is rare in these studies [9-11]. Macgowan *et al*. [6] reported that adequate energy and protein delivery is possible in patients receiving VV-ECMO support. Hardy *et al*. [12] also stated that VV-ECMO was not a barrier to nutritional adequacy in COVID-19 patients. This variation reflects the need for further research and consensus in order to provide standardized guidelines and best practices for implementing optimal nutrition to patients undergoing VV-ECMO [6, 12].

The nutritional support can be challenging in patients with ARDS who receive VV-ECMO. This is likely because VV-ECMO can cause gastrointestinal disturbances, such as nausea, vomiting, and diarrhea. These disturbances can make it difficult to provide patients with adequate nutrition through EN. Therefore, it is important to monitor critically ill patients who receive VV-ECMO for nutritional problems. Early identification and intervention can help to prevent complications and improve outcomes. In addition, there are a few studies comparing nutritional adequacy and problems in critically ill patients who received VV-ECMO to those who did not.

This study aimed to describe the nutritional care, adequacy of nutrition, and clinical outcomes of providing nutritional support and to compare these in patients with ARDS who received VV-ECMO with those who did not.

METHODS

A retrospective observational study of adult patients with ARDS receiving and not receiving VV-ECMO was undertaken on our mixed medical and surgical ICUs. This study was approved by the Hospital's Medical Ethics Committee (The decision number is 2022-15/2) and conducted in accordance with the principles of the Declaration of Helsinki.

Participants and Study Groups

Our hospital has a total of 189 adult intensive care beds, 61 of which are under the responsibility of anesthesiologists and intensive care specialists. Patients (age > 18 years) with severe ARDS receiving VV-ECMO (≥ 72 h) between January 1, 2021 to October 31, 2022 were included in the study. Patients with severe ARDS who did not receive VV-ECMO between the same period were included as the control group. ECMO patients were analyzed while forming the control group, and they were formed from patients with similar age, gender and comorbidities. The diagnosis of severe ARDS was made according to the Berlin Definition [13]. Patients were excluded if there was not any documentation about calculated nutritional targets. Pregnant women, end-stage cancer patients, and patients who stayed in the ICU for less than 24 hours were also excluded from the study.

Nutrition Support Protocol

All patients in the study received nutritional therapy according to our ICU's standard protocols. Our ICU's standard protocols are based on the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [14]. Medical nutrition therapy is considered for all patients staying in the ICU for more than 48 hours. Our aim is to begin nutritional therapy

through a nasogastric (NG) tube within 24 hours of the patient's admission to the ICU. Afterwards, individualized nutritional goals were calculated by the ICU dietitians and physicians within 48-72 hours. In patients who do not tolerate full-dose EN during the first week in the ICU, the safety, and the benefits of initiating parenteral nutrition (PN) are being evaluated on an individual basis. Since we have no indirect calorimetry, a simple equation based on weight is used for energy calculation. While the energy target is 20-25 kcal/kg/day in the acute disease period, it is calculated as 25-30 kcal/kg/day in the anabolic period. While hypocaloric nutrition is preferred in the early stage of acute disease, nutritional support is increased by 80-100% of the calculated energy after 3 days. Daily protein requirements are estimated to be at least 1.3 g/kg considering the actual body weight. If the patient's body mass index (BMI) is > 25 kg/m^2, ideal body weight is considered in target protein and energy calculations.

Data Collection

Data were collected for each patient's sex, BMI, the number of days of ECMO support, the number of invasive mechanical ventilation (IMV) days, length of ICU, and hospital stay were collected via an electronic medical record and nurse patient follow-up forms. The severity of critical illness was calculated using Acute Physiology and Chronic Health Evaluation (APACHE) II and NUTrition Risk in Critically ill (NUTRIC) score on the day of ICU admission. Additionally, the NUTRIC score was calculated when the patients were intubated. The degree of organ failure was evaluated using by the Sequential Organ Failure Assessment (SOFA) score. In the VV-ECMO group, the SOFA score was calculated at admission to the ICU and on the 1st day of ECMO. In the non-ECMO group, the SOFA score was calculated at admission to the ICU. The daily achievement of the energy target (in percentage) and the daily average protein intake were calculated during the first 2 weeks after the initiation of VV-ECMO, or until death if it occurred within 2 weeks. In patients who did not receive VV-ECMO, daily achievement (%) of the energy target and mean daily protein intake were calculated for 2 weeks after intubation, or for the period until death if the patients died within 2 weeks. Underfeeding was defined as < 80% of the target of energy or protein intake for that day, and overfeeding was defined as receiving > 110% of energy targets. Propofol was not included in the energy calculation because only 1 of the patients included in the study received short-term propofol infusion.

The primary outcome is whether we can give adequate calories to patients receiving VV-ECMO compared with those who do not. We also determined the reasons for hypocaloric underfeeding and discontinuation of EN and outcome of patients.

Statistical Analysis

The data were analyzed using SPSS software (version 20.0) and Graphpad Prism 8. The descriptive statistics are presented as number, percentage, mean ± SD, and median with minimum-maximum value. The normal distribution of the data of the numerical variables was evaluated using the Shapiro-Wilk normality test. Comparisons between groups were performed with a t -test for variables with normal distribution and the Mann–Whitney U test for variables without normal distribution. The relationships between categorical data were evaluated using the chi-square test. Friedman test was used to compare the data at different individual time points. To determine which pairs are different, a pairwise comparison test was carried out. $P < 0.05$ was considered statistically significant.

RESULTS

In this study, 24 patients were included, of whom 12 received VV-ECMO (Fig 1). The patients were divided into two groups, received VV-ECMO (10 men; mean age, 46.4 years) and not received VV-ECMO (7 male; mean age, 51.8 years). The mean APACHE II, SOFA and NUTRIC scores in all patients were 12.71 ± 6.59, 4.71 ± 1.57 and 2.63 ± 1.58, respectively. The median value of PaO2/FiO2 (P/F) ratios was 76.96 ± 21.78. There was no difference between groups in terms of age, gender, ICU scores, and P/F ratio. The mean duration between intubation and start to VV-ECMO was 6.83 ± 11.12 days. The mean duration of ECMO support was 13.08 ± 4.03 days. Two patients (16.6%) were weaned off ECMO.

Mechanical ventilation duration was longer in the

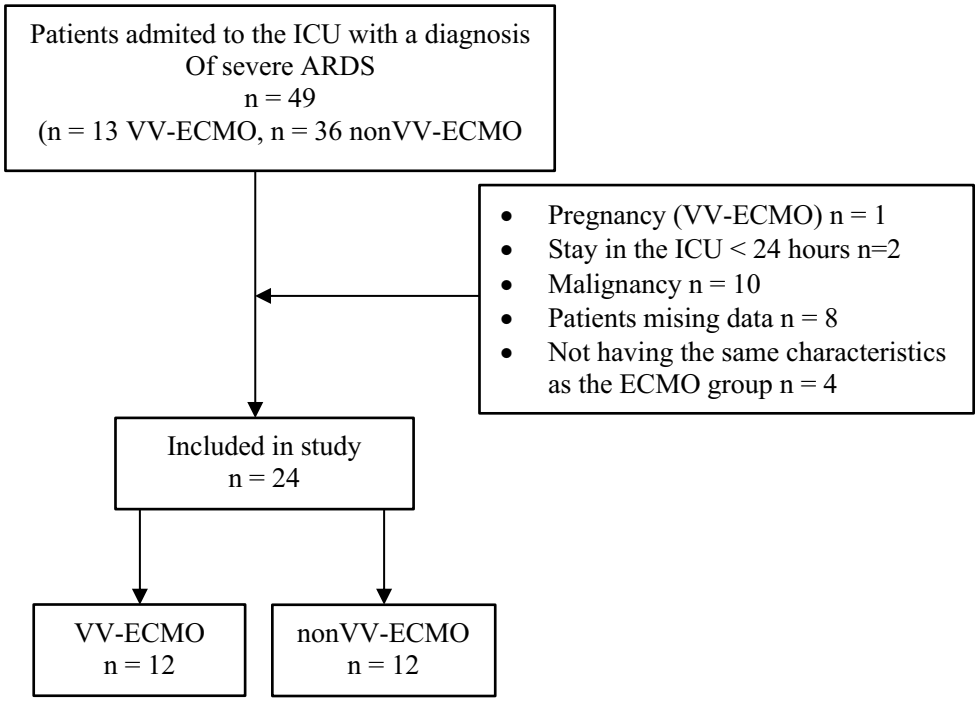

Fig. 1. Flow diagram of the study.
ICU = Intensive Care Unit, VV-ECMO = Veno-Venous Extra-Corporeal Membrane Oxygenation.

VV-ECMO group than non-ECMO group ($p = 0.045$). The length of stay (LOS) in the ICU was 34.42 ± 24.33 days in the VV-ECMO group and 20.33 ± 10.5 day in the non-ECMO group ($p = 0.079$). Mortality was high in both the groups (83.3% in VV-ECMO group, 91.7% in non-ECMO group). The baseline characteristics and ICU treatments of both groups are summarized in Table 1.

Nutrition Support

Continuous EN was first administered to all patients by the NG route. The median time to start enteral feeding was 1 days in all patients, and the mean time to reach 80% of the daily calorie goal was 3.92 ± 3.13 days. In the VV-ECMO group, the mean target calories and protein were 1583 ± 158.59 kcal/day and 100.42 ± 10.75 gr/day, respectively. The mean target calories and protein were similar in both groups ($p = 0.915$ and $p = 0.931$, respectively). In the VV-ECMO group, 75% of the patients could achieve nutritional adequacy (> 80% energy goal) and 83.3% in the non-ECMO group ($p = 0.615$). The average energy delivered to the VV-ECMO group was 73% of the targeted energy. However, the average energy delivered to the non-VV ECMO group was 82% of the targeted energy. There was no significant difference between groups ($p = 0.233$) (Fig. 2). In the VV-ECMO group, the energy delivery rate increased from 1st day's 31% to 67% of their nutritional goal on the third day. By the end of 1st week 82% of the nutritional goal was reached. The increase in energy delivery from day 1 to day 7 was significant ($p = 0.043$). On the other hand, in the non-ECMO group, the energy delivery rate increased from 1st day's 49% to 92% of their nutritional goal by the third day. By the end of 1st week 83% of the nutritional goal was reached. Although the targeted energy level was reached, the increase in energy delivery from day 1 to day 7 was not significant ($p = 0.393$) (Fig. 3).

When we analyzed the protein targets, although they were similar in both groups, target protein (> 80% protein goal) could be given in only 6 (50%) patients in both groups. The protein delivery percentage was below the targeted level in both groups (Figs. 2 and3). The enteral feed was administered polymeric in 23 patients and olymeric diet in 1 patient. Most diets contained 1 kcal/mL. The used polymeric products was 500 ml which contained an average of 26 g of protein.

Table 1. Baseline characteristics of all patients and comparison of groups

	All patients (n = 24)	VV-ECMO Group (n = 12)	non-ECMO Group (n = 12)	*p* value
Age (years)	49.08 ± 12.37	46.42 ± 11.53	51.83 ± 13.1	0.294
Gender, n (%)				
Male	17 (70.8)	10 (83.3)	7 (58.3)	0.178
APACHE II score	12.71 ± 6.59	12.33 ± 8.47	13.08 ± 4.31	0.787
SOFA score	4.71 ± 1.57	4.75 ± 1.71	4.67±1.49	0.9
NUTRIC score	2.63 ± 1.58	2.5 ± 1.78	2.75 ± 1.42	0.708
BMI (kg/m^2)	27.62 ± 3.10	27.27 ± 2.9	27.98 ± 3.36	0.587
Duration between admission to ICU and intubation (days)	6 ± 4.37	7.33 ± 4.84	4.67 ± 3.55	0.139
Duration between onset of symptoms and intubation (days)	11.92 ± 7.98	15.3 ± 8.04	8.5 ± 6.55	**0.033**
PaO2/FiO2- ICU on admission	76.96 ± 21.78	76.33 ± 25.03	77.58 ± 19.09	0.892
PaO2/FiO2- First day of intubation	70.67 ± 18.02	72.58 ± 13.79	70.67 ± 18.02	0.773
Co-morbidites, n (%)				
Diabetes mellitus	6 (25)	5 (41.7)	1 (8.3)	0.059
Hypertension	8 (33.3)	4 (33.3)	4 (33.3)	1
Treatments in ICU, n (%)				
CRRT	6 (25)	5 (41.7)	1 (8.3)	0.059
Vasopressors	16 (66.7)	10 (83.3)	6 (50)	0.083
Proning, n (%)	8 (33.3)	1 (8.3)	7 (58.3)	**0.009**
IMV (days)	18.29 ± 11.42	18.5 (6-45)	11 (7-24)	**0.045**
ICU (days)	27.38 ± 19.68	34.42 ± 24.33	20.33 ± 10.5	0.079
Hospital satay (days)	35.29 ± 27.87	44 ± 35.87	26.58 ± 13.13	0.129
Mortality, n (%)	21 (87.5)	10 (83.3)	11 (91.7)	0.537

Data are shown as mean±standard deviation or median (minimum-maximum or number (percent). VV-ECMO = Veno-Venous Extra-Corporeal Membrane Oxygenation, APACHE = Acute Physiology and Chronic Health Evaluation, SOFA = Sequential Organ Failure Assessment, NUTRIC = NUTrition Risk in Critically ill, BMI = Body Mass Index, = ICU Intensive Care Unit, CRRT = Continuous Renal Replacement Therapy, IMV = Invasive Mechanical Ventilation

When we examined the reasons of inadequate EN application, the most common reason was the prone position. Calories received during proning were reduced in 4 (33.3%) patients in the non-ECMO group. Hemodynamic instability was detected in 2 patients in the VV-ECMO group and in 1 patient in the non-ECMO group. Hemodynamic instability was considered if the shock was uncontrolled and the hemodynamic and tissue perfusion targets were not achieved with vasopressors/inotropes (MAP < 65 mmHg, lactate > 2 mmol/L, signs of insufficient tissue perfusion). While upper digestive intolerance was not detected in any patient in the non-ECMO group, it developed in 2 (16.7%) patients in the VV-ECMO group. Vomiting was not observed in these 2 patients although the gastric residual volume (GRV) was >500 mL. Parenteral nutrition was used to complement nutrition requirements in case of underfeeding with EN in 4 patients in the VV-ECMO group and 3 patients in the non-ECMO group. The nutritional interventions of the patients are shown in Table 2.

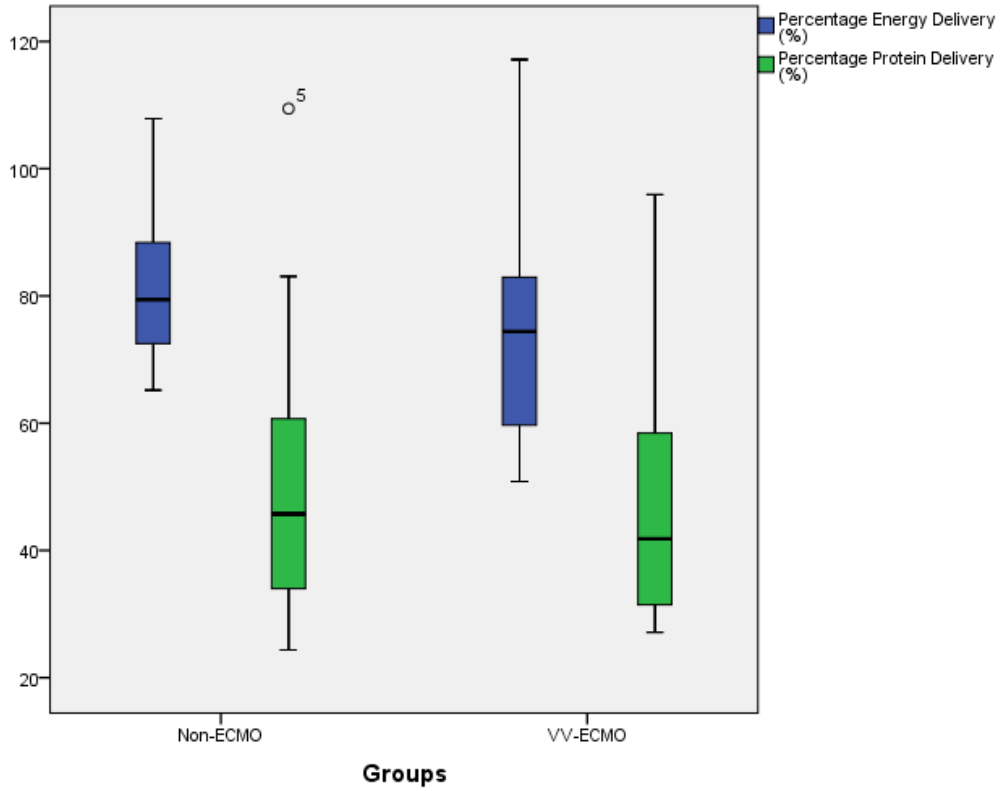

Fig. 2. Energy and protein delivery.
Figure shows the percentage delivery of total energy and the protein. Box plot indicates mean values. Whiskers indicate minimum and maximum values. No statistical significance between groups according to the percentage delivery of total energy and the protein (p = 0.233 and p = 0.735 respectively).

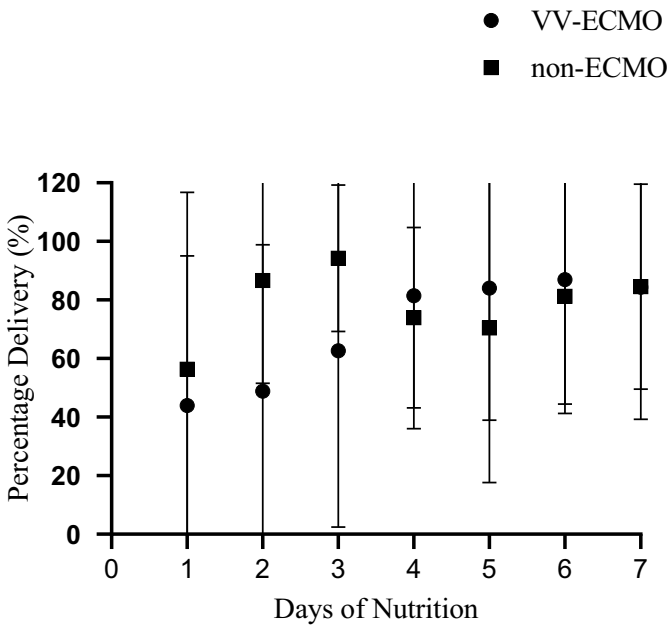

Fig. 3. Daily energy delivery for the first 7 days.
Figure shows the daily percentage delivery of total energy (including all sources) for the first 7 days. Box plot indicates mean values. Whiskers indicate minimum and maximum values. VV-ECMO = Veno-Venous Extra-Corporeal Membrane Oxygenation.

Tablo 2. The nutritional interventions by groups

	All patients (n = 24)	VV-ECMO Group (n = 12)	non-ECMO Group (n = 12)	*p* value
Time to start EN (days)	1 (1-4)	1.5 (1-4)	1 (1-2)	0.303
80% of measured energy targets (days)	3.92 ± 3.13	4.58 ± 3.77	3.25 ± 2.30	0.308
Energy target (kcal)	1587.50 ± 184.89	1583 ± 158.59	1591 ± 215.146	0.915
Protein target (g)	100.21 ± 11.46	100.42 ± 10.75	100.0 ± 12.61	0.931
Max. protein delivery (days)	6.67 ± 2.74	6.33 ± 3.37	7 ± 3.07	0.564
Max. energy delivery (days)	7.21 ± 2.93	7.33 ± 2.80	7.08 ± 3.17	0.84
Patients achieving 80% of their energy goal, n (%)	19 (79.2)	9 (75)	10 (83.3)	0.615
Patients achieving 80% of their protein goal, n (%)	12 (50)	6 (50)	6 (50)	1
Time to start PN (days)	5 ± 2.12	5.40 ± 2.51	4.5 ± 1.73	0.563
Parenteral nutrition, n (%)	7 (29.2)	4 (33.3)	3 (25)	0.254
Reasons for inadequate EN, n (%)				0.119
Hemodynamic instabilit	3 (12.5)	2 (16.7)	1 (8.3)	
Pronin	4 (16.6)	0	4 (33.3)	
Gastric distention	2 (8.4)	2 (16.7)	0	
Diarrhea	1 (4.2)	1 (8.3)	0	

Data are shown as mean ± standard deviation or median (minimum-maximum or number (percent). VV-ECMO = Veno-Venous Extra-Corporeal Membrane Oxygenation, EN = Enteral Nutrition, PN = Paranteral Nutrition

DISCUSSION

In this study, we described the nutritional practices in patients with ARDS supported by VV-ECMO at a single center. We think that VV-ECMO was not an obstacle for adequate nutrition provision in critically ill patient. However, the prone position was a frequent reason for enteral feed interruptions and inadequate energy delivery. To our knowledge, our study is one of a limited number of studies describing nutritional adequacy and problems in critically ill patients, which compares a cohort receiving VV-ECMO with a non-ECMO cohort.

Nutrition guidelines recommend early EN in critically ill patients unable to maintain adequate intake [14, 15]. Physicians may be reluctant to initiate enteral feeding because of concerns about complications such as delayed gastric emptying and non-occlusive mesenteric ischemia. In our study, enteral nutrition was started in the early period (< 48 hours) in the VV-ECMO group, as in the non-ECMO group. Additionally, the time to reach 80% of the calculated energy was similar in both groups. Besides, the percentage of energy supply on the 7th day in both groups was quite satisfactory (Group VV-ECMO 73%, group non-ECMO 81%). In the VV-ECMO group, 9 (75%) patients achieved of their energy goals and 10 (83.3%) in the non-ECMO group. Lukas *et al*. [16] detected that the mean nutritional adequacy during ECMO support was 55%, which was lower than that of general ICU patients. On the other hand, in the study by Hardy *et al*. [12] the rate of achieving the energy goal was high (81%) in patients receiving VV-ECMO similar to ours. In another study, it was reported that 80% of 102 patients who underwent VA-ECMO tolerated EN [17]. In our study, the finding of similar energy delivery with enteral feeding in VV-ECMO compared with the non-ECMO cohort is promising. However, the target protein was reached in 50% of the patients in both groups. Weijs *et al*. [18] found that ICU patients with

1.2-1.5 g/kg/day delivered protein had reduced 28-day mortality. Compher *et al*. [19] reported that the odds of death decreased by 6.6% with each 10% increase in protein intake. Although we cannot attribute the high mortality rate in our study solely to protein deficiency, we think that insufficient protein intake may be a contributing factor to high mortality. A reason for inadequate protein support was the low protein content of the enteral products used and the lack of products to provide additional protein support in our hospital.

Enteral nutrition was initiated using the gastric route as recommended in the guidelines [14, 15]. In addition, NG feeding is the most common route for nutritional support reported in studies of patients undergoing ECMO [3,17]. The administration of continuous versus bolus feeds is an important matter to address. Current studies suggest that bolus and continuous enteral feeding can achieve the same goal in critically ill patients without an increase in side effects in either of these pathways [20-22]. In this study, continuous EN was administered to all patients through the NG route.

The best timing to prescribe supplemental PN remains debated. The ESPEN 2019 guidelines recommended that those who do not tolerate a full dose of EN during the first week in the ICU should be considered for additional PN [14]. In our study, PN was initiated in approximately 5.4 days in the VV-ECMO group and approximately 4 days in the non-ECMO group. PN support was applied in 33.3% of the patients in the VV-ECMO group and 25% in the non-ECMO group. In the literature, the reported use of PN in patients receiving ECMO support ranged from 4% to 30% [3]. In our study, the use of PN was similar to the literature.

Patients undergoing ECMO may have circulatory shock, requiring vasoactive agents. While guidelines on nutritional support in critically hemodynamically stable patients share a common recommendation, there is no consensus in hemodynamically unstable patients [14, 15]. Although critical care providers may be reluctant to initiate EN early in circulatory shock, recent randomized controlled trials have shown that early initiation of low-dose EN is associated with improved clinical outcomes [23]. In this study, early low-dose EN was initiated in 3 patients with hemodynamic failure (VV-ECMO group 2 patients, non-ECMO 1 patient), and no adverse complications related to nutrition were detected.

Studies have highlighted increased GRV as one of the most common causes of EN interruption during ECMO [10, 25]. Mentec *et al*. [25] found that 49 (32%) of critically ill patients had an increase in GRV after a median EN duration of 2 days. In addition, sedation and use of catecholamines before and during EN have been reported to be risk factors for increased GRV. Increased GRV was detected in 2 patients in the VV-ECMO group, and vomiting was not observed in these patients.

In our study, the most common reason for the interruption of EN in the non-ECMO group was the prone position. EN volumes were considerably lower in these patients, resulting in underfeeding. Saez de la Fuente *et al*. [26] reported that EN was not associated with an increased risk of gastrointestinal complications in critically ill patients with severe hypoxemia receiving mechanical ventilation in the prone position. However, Reignier *et al*. [27] documented an incidence rate of 82% for the development of EN intolerance in the prone position. Studies supporting the safety of EN in the prone position are needed.

In studies evaluating the safety, tolerability, and results of EN during ECMO, the rate of development of intestinal ischemia has been reported to be quite low [11, 24, 28-31]. These studies have suggested that intestinal ischemia is associated with disease severity, and it has been reported that these patients have high APACHE II and SOFA scores [24, 29]. We did not detect bowel ischemia in any patient in our study. In our study, the patients were in young population who received VV-ECMO due to hypoxemia and the severity of illness scores (APACHE and SOFA) were low.

The mortality rate was high in our study. The Berlin Definition was developed in 2012, which categorizes ARDS as mild, moderate, or severe based on the degree of hypoxemia [13]. When our patients were evaluated according to the Berlin Definition, they were in the severe ARDS classification. The P/F ratios of patients in both groups were < 100 mmHg. Previous studies were reported that ICU and hospital survival decreased when ARDS severity increased [32, 33].

Limitations

Our study compares nutritional support in patients with and without VV-ECMO. However, the limitations of our study include being a single-center retro-

spective study and having a small number of patients. Another limitation is that the energy needs of the patients are calculated by the dietitian and clinician, and no indirect calorimetry was used.

CONCLUSION

ICU stays prolonged in patients undergoing ECMO. Additionally, these patients have more severe organ dysfunction. Considering these conditions, although the risk of acquiring malnutrition increases, guideline recommendations for the nutrition of patients undergoing ECMO are insufficient. Our results suggest that adequate energy and protein delivery is possible for most patients during VV-ECMO. Stronger randomized controlled trial-level evidence is needed to provide adequate nutritional care in patients undergoing ECMO.

Authors' Contribution

Study Conception: GÇ; Study Design: GÇ, NKG; Supervision: GÇ, NKG; Funding: N/A; Materials: N/A; Data Collection and/or Processing: GÇ; Statistical Analysis and/or Data Interpretation: GÇ; Literature Review: GÇ, NKG; Manuscript Preparation: GÇ, NKG and Critical Review: GÇ, NKG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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