Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Safety and tolerance of enteral nutrition in COVID-19 critically ill patients, a retrospective study

Iván Osuna-Padilla, Nadia Carolina Rodríguez-Moguel, Adriana Aguilar-Vargas*, Sebastián Rodríguez-Llamazares

Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, México City, Mexico

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SUMMARY

Background: There is a lack of evidence about the tolerance of enteral nutrition (EN) in COVID-19 critically ill patients. However, several gastrointestinal manifestations related to COVID-19 have been described. The aims of this study were to analyze the incidence of gastrointestinal intolerance (GI) associated to EN (diarrhea, vomiting, gastroparesis and constipation) and to describe energy/protein provision along with biochemical alterations during the first week of EN.

Methods: A retrospective cohort of COVID-19 critically ill patients under mechanical ventilation. We reported daily enteral nutrition infusion and gastrointestinal manifestations within the first week of intubation and enteral nutrition initiation.

Results: Fifty-two patients were included; 40.3% were overweight and 46.2% were obese. During the first 7 days of EN, manifestations of GI intolerance such as vomiting, diarrhea and gastroparesis were present in 18 patients (32.4%). Hypernatremia (39%) was the most frequent electrolyte abnormality. Only Acute Kidney Injury (AKI) diagnosis was associated with a higher energy deficit on day 7. No associations between drug prescription and GI intolerance were observed. On day 4, 94.5% of patients were receiving more than 80% of energy requirements and 94.2% of protein requirements. Accumulated energy and protein deficits at day 3 were 2171.2 ± 945 kcal and 114.9 ± 49.2 g, respectively; and 2586.4 ± 1151 kcal, 133.3 ± 60.4 g at day 7.

Conclusion: Enteral nutrition is feasible and well-tolerated in COVID-19 patients with mechanical ventilation within the first week of enteral nutrition initiation. More studies are needed to elucidate the impact of nutritional therapy on infection course and outcomes.

1. Background

Worldwide, as of January 2021, over ninety three million patients have been affected by Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 [1]. Studies have shown that nearly 30% of hospitalized patients require admission n to intensive care units (ICUs) for ventilatory support [2].

Nutritional support should be started in the critically ill patient due to the inability to use the oral route during mechanical ventilation [3,4]. Enteral nutrition (EN) should be preferred over parenteral nutrition since it has been associated with a lower incidence of infectious complications, fewer days of hospital stay, and mortality reduction in previous meta-analyses [5].

In COVID-19 patients, early EN initiation in the first 24–48 h after ICU admission or within 12 h after mechanical ventilation is indicated, as proposed by the Academy of Nutrition and Dietetics (AND), the American Society for Parenteral and Enteral Nutrition (ASPEN), European Society for Clinical Nutrition and Metabolism (ESPEN) and Australian Society of Parenteral and Enteral Nutrition (AuSPEN) [6–9]. Prior to the pandemic, evidence supports role of early EN in gut integrity maintenance through multiple mechanisms, which may contribute to limit microbial translocation and systemic inflammation [3]. Furthermore, proper timing of nutritional therapy, and optimal dosing of nutrients, considering amounts of energy from drips and medications [10], should be prescribed to prevent malnutrition and metabolic alterations. Delay and interruptions in enteral feeding, mainly associated with GI

* Corresponding author. Centro de Investigaciones en Enfermedades Infecciosas, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Calz, Tlalpan 4502, CP 14080, Mexico City, Mexico.
E-mail address: adriana.aguilar@cieni.org.mx (A. Aguilar-Vargas).

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dysfunction, impact the achievement of nutritional targets and impairs overall nutritional status.

However, early initiation of EN has been associated with gastrointestinal (GI) intolerance and vomiting in 30–70% of ICU patients, as well as gut ischemia in critically ill patients with shock [11]. Thus, GI intolerance may be a reason for EN contraindication and parenteral nutrition initiation [6]. Additionally, early EN initiation may be delayed by vasopressor therapy dosage in case of hemodynamic instability, which is characterized by hypovolemia, hypotension, hyperlactatemia and tissular hypoperfusion, which can also increase the risk of gastrointestinal intolerance [11]. In a cross-sectional study of COVID-19 non-critically ill patients, 20.5% reported at least one gastrointestinal symptom. At the onset of infection, the most common manifestations were diarrhea (17.8%), abdominal pain (9.8%), and vomiting (7.1%) [12]. Although this might influence clinical decisions regarding EN initiation, there is a lack of evidence about safety and tolerance of enteral nutrition specifically in COVID-19 critically ill patients.

The aims of this study were to analyze the incidence of gastrointestinal intolerance associated to EN (diarrhea, vomiting, gastroparesis and constipation) during the first week, and to evaluate associations between clinical and laboratory data with GI intolerance and energy-protein deficits in critically ill patients receiving mechanical ventilation due to confirmed COVID-19.

2. Methods

In a retrospective cohort study, we included critically ill patients over 18 years old with a documented diagnosis of COVID-19 requiring mechanical ventilation from March 1 2020 to June 30 2020 in the National Institute of Respiratory Diseases, a tertiary-care hospital in Mexico City, Mexico. For inclusion, COVID-19 diagnosis was confirmed by both RT-PCR for SARS-CoV2 and suggestive tomographic findings. Patients with unavailable data of time of initiation and prescription of EN, as well as patients that required less than 48 h of mechanical ventilation were excluded. A total of 137 patients were screened during the study period, only 52 patients were included in the analysis (Fig. 1). This study was reviewed and approved by the Institutional Review Board of the National Institute of Respiratory Diseases (Register #C51-20).

2.1. Data collection

From patient records, demographic information including sex, age, height, weight, and body mass index (BMI) were collected. Prescribed drugs with nutritional implications (steroids, benzodiazepines, opioids, neuromuscular blocking agents (NBA), sedatives, dexmedetomidine, insulin regimen and vasopressors), as well as PaO_2/FiO_2 ratio, medical history of non-communicable diseases and biochemical parameters (acid-base status, electrolytes, glucose, and lipid levels) were also registered. APACHE II and SOFA scales were calculated at first day of nutritional assessment within 24 h of hospital admission. From nursing charts, we recollected diet infusion, stool output, gastric residual volume, abdominal distention and vomiting. Clinical outcomes (length of stay, length of ventilation and mortality) were also reported.

2.2. Enteral nutrition prescription

Orogastric tubes were inserted as part of routine clinical care for mechanically ventilated patients. Orogastric tube placement was used over other short-term accesses as a common Institutional practice to avoid epistaxis and sinus infection. Following radiographic confirmation of the correct tip position, patients were evaluated by a team of certified ICU dietitians. Calories and protein

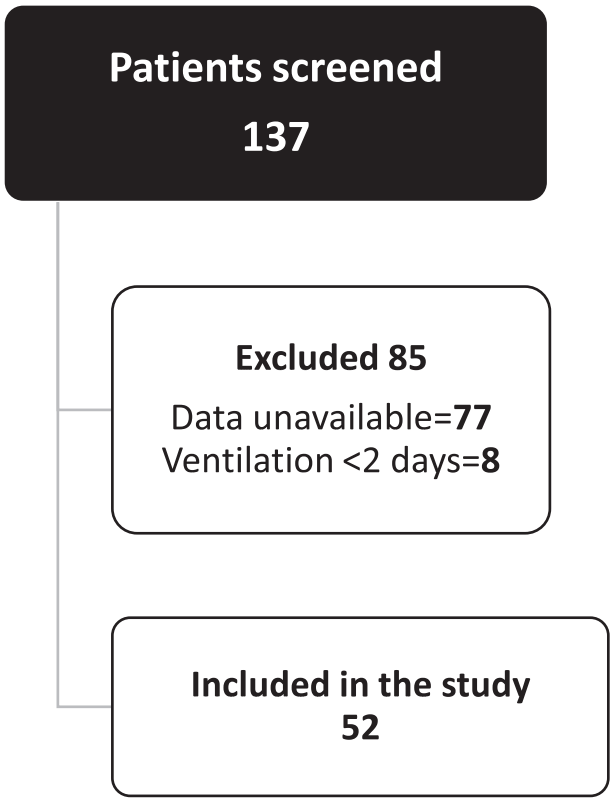

Fig. 1. Flowchart study-overview.

were prescribed according to recommendations by the American Society of Parenteral and Enteral Nutrition (ASPEN) and European Society for Clinical Nutrition and Metabolism (ESPEN), with a general target of 25 kcal/kg and 1.3 g/kg, respectively [7,8]. Ideal body weight was used in patients with a BMI>30 kg/m^2 and was calculated using Hamwi equations. Calories derived from non-nutritional sources were factored into the nutrition prescriptions in order to avoid overfeeding. Enteral feed products were prescribed using standard and specialized polymeric formulas, according to each patient's individual needs. The enteral nutrition regimen consisted of the total volume of feed administered over 18 h, as per local feeding protocols.

2.3. Safety of enteral nutrition provision

Energy and protein prescription and provision were daily recorded. Total provided energy was calculated from glucose/propofol infusions and EN prescriptions. The daily achievement of an energy target (%) and the daily average protein provision during the first week after mechanical ventilation were calculated. The cumulative deficit was also calculated for day 3 and day 7. The adequate nutritional threshold was set at > 80% of prescribed targets [14]. Causes for interruptions in enteral nutrition feeding were registered and classified as hemodynamic instability, medical procedures, gastrointestinal intolerance, or unjustified reasons. Incidence of gastrointestinal intolerance was recorded; diarrhea (frequency of bowel movement > 3–5 times/day or liquid stools), vomiting, constipation (no evacuation during 6 consecutive days) and gastroparesis (gastric residual volume >300 ml) [15,16]. The latter corresponds to the cut-off point used in our institution to decide prokinetic administration to improve gastric emptying. Metabolic alterations during first 7 days of EN were also registered;

hypokalemia (K < 3.5 mmol/L), hyperkalemia (≥5 mmol/L), hypophosphatemia (<0.81 mmol/L), hypomagnesemia (<0.65 mmol/L), hypernatremia (≥145 mmol/L), hyperlactatemia (>2 mmol/L) and hyperglycemia (>10 mmol/L).

2.4. Statistical analysis

All statistical analyses were performed using STATA software, version 14. Shapiro–Wilk test was employed to determine whether the variables were normally distributed. Categorical variables were expressed as frequency rates (%), and continuous variables were expressed as means (standard deviation) or median and interquartile range (IQR) values (P_{25}–P_{75}). Means for continuous variables were compared using independent group t-test when the data were normally or using the Mann–Whitney U test otherwise. Proportions for categorical variables were compared by χ^2 test between two groups. Energy and protein deficit at day 7 was dichotomized (yes/no) according to the mean observed in the sample (2586.4 kcal or 133.3 g, respectively). Gastrointestinal intolerance was operationalized as any gastrointestinal sign or symptoms during the first 7 days of EN. Logistic regression models were used to analyze the associations between clinical diagnosis and drug prescriptions with energy-protein deficits and GI intolerance during the first 7 days of EN, adjusted to age and SOFA scale. A p-value <0.05 was considered statistically significant.

3. Results

The demographic characteristics and clinical features of patients are displayed in Table 1. The average age was 55.7 ± 14.3 years old, 33% being over 60 years. There was a male predominance overall (83%), and the mean age of females (65.1 ± 17.8 years) was significantly higher than that of males (53.7 ± 12.9 years; p < 0.02). The average BMI of patients was 29.5 ± 4.4; 40% were overweight and 46% were obese. The most common comorbidities were diabetes (39%) and hypertension (37%). The mean APACHE II and SOFA scores were 21 ± 5 and 9 ± 2, respectively. Any degree of acute kidney injury was diagnosed in 21 (40%) patients.

While none of the patients required parenteral nutrition, only 2 patients did not receive enteral nutrition the first 3 days, starting until day 4. During the first week of hospital stay, patients received some drugs that affect nutrients' metabolism and gastrointestinal motility (described in Table 1). A total of 30 patients (57%) died. Surviving patients were ventilated for 15.5 (9–25) days for an overall length of stay of 27.5 (16–41) days.

Table 1
Demographics, clinical and nutritional characteristics of COVID-19 critically-ill patients.

	n = 52
Age, years	55.7 ± 14.3
30–40 years	9 (17%)
40–50 years	9 (17%)
50–60 years	17 (33%)
60–70 years	9 (17%)
70–80 years	5 (10%)
>80 years	3 (6%)
Sex (%)	
Male	43 (83%)
Female	9 (17%)
Weight (kg)	79.7 ± 14.7
Ideal body weight (kg)	60.0 ± 7.9
Body mass index (kg/m^2)	29.5 ± 4.4
Normal weight 18.5–24.9 kg/m^2	7 (14%)
Overweight 25–29.9 kg/m^2	21 (40%)
Obesity >30 kg/m^2	24 (46%)
Comorbidities (%)	
Diabetes	20 (39%)
Hypertension	19 (37%)
Diabetes + Hypertension	10 (19%)
COPD	2 (4%)
Disease Severity	
PaO_2/FiO_2 Ratio	131 (96–166)
SOFA Score	9 ± 2
APACHE II Score	21 ± 5
Acute Kidney Injury (%)	21 (40%)
Renal Replacement Therapy (%)	4 (8%)
Prescribed Drugs	
Steroids	32 (63%)
Benzodiazepines	45 (87%)
Opioids	52 (100%)
Neuromuscular blocking agents	38 (73%)
Propofol	13 (25%)
Dexmedetomidine	6 (12%)
Rapid-acting insulin regimen	30 (58%)
NPH Insulin with rapid-acting regimen	13 (25%)
Vasopressors	22 (42%)
Enteral nutrition prescription	
Energy (kcal/day)	1502.4 ± 199
Protein (g/day)	78.1 ± 10.3
Cumulative energy and protein deficit	
Energy deficit day 3 (kcal)	2171.2 ± 945
Energy deficit day 7 (kcal)	2586.4 ± 1151
Protein deficit day 3 (g)	114.9 ± 49.2
Protein deficit day 7 (g)	133.3 ± 60.4
Clinical outcomes	
Length of ventilation	15.5 (9–25)
Length of stay (discharge)	27.5 (16–41)
Length of stay (died)	14 (8.5–26)
Mortality	30 (57%)

Mean ± SD, Median (IQR), n (%).

3.1. Enteral nutrition interruption and gastrointestinal tolerance

Gastrointestinal intolerance manifestations like vomiting, diarrhea, and gastroparesis were present in 18 patients (35%) at any moment during the first 7 days of EN (Table 2). The incidence of constipation was found in 45 (87%) patients. Hemodynamic instability was the main reason (64%) to avoid EN delivery during the first 24 h of mechanical ventilation. Interruptions due to GI intolerance were documented in 11 patients during the first week of EN (Table 3).

3.2. Energy provision from enteral nutrition and non-nutritional sources

Adequacy of enteral nutrition, defined as provision >80% of energy and protein requirements, was assessed daily. Considering non-nutritional sources, the percentage of patients with acceptable adequacy was 94.5% for energy and 94.2% for protein provision on day 4. High energy supply from non-nutritional sources (propofol and dextrose) were observed on the third day (103 kcal/day), amounts that gradually decreased to 80 kcal on day 7. Accumulated energy and protein deficits at day 3 were 2171.2 ± 945 kcal and 114.9 ± 49.2 g, respectively, and 2586.4 ± 1151 kcal, 133.3 ± 60.4 g at day 7.

3.3. Biochemical alterations

Laboratory alterations were collected and are reported in Table 4. During the first week of mechanical ventilation, glucose concentrations were above the normal range (>10 mmol/L) in 46% of patients. Hypernatremia was the most frequent electrolyte abnormality. Incidence of hypokalemia, hypomagnesemia, and hypophosphatemia was observed in 7%, 4%, and 9% of patients, respectively.

Table 2
Number of GI intolerance episodes during the first 7 days of mechanical ventilation.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Week
Gastrointestinal intolerance (n = 52)	0 (0%)	4 (8%)	7 (13%)	3 (7%)	5 (10%)	3 (6%)	5 (10%)	18 (35%)
Type								
Gastroparesis	0	2	3	2	2	2	2	13 (25%)
Vomiting	0	2	2	0	1	0	1	6 (11%)
Diarrhea	0	0	2	1	2	1	2	8 (15%)

n (%); Gastroparesis (gastric residual volume >300 ml); Diarrhea (frequency of bowel movement > 3–5 times/day or liquid stools).

Table 3
Causes of enteral nutrition interruption during the first week of mechanical ventilation.

	Main reasons (n = 52)			
	Hemodynamic instability	Gastrointestinal intolerance	Medical procedures	No reason
Day 1	33 (64%)	1 (2%)	–	–
Day 2	4 (8%)	1 (2%)	–	1 (2%)
Day 3	–	3 (6%)	1 (2%)	–
Day 4	–	–	–	–
Day 5	1 (2%)	1 (2%)	–	–
Day 6	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Day 7	1 (2%)	4 (8%)	–	1 (2%)

n (%).

Table 4
Number of patients with biochemical alterations during the first 7 days of mechanical ventilation.

Biochemical n = 52	Day 1 n (%)	Day 2 n (%)	Day 3 n (%)	Day 4 n (%)	Day 5 n (%)	Day 6 n (%)	Day 7 n (%)	Week (%)
↑Na	9 (17)	13 (25)	27 (52)	27 (52%)	28 (54)	23 (44)	15 (29)	39%
↓K	2 (4)	3 (6)	3 (6)	2 (4)	7 (13)	3 (6)	4 (8)	7%
↑K	10 (19)	10 (19)	6 (12)	6 (12)	3 (6)	2 (4)	4 (8)	11%
↓Mg	3 (6)	2 (4)	1 (3)	2 (4)	5 (10)	1 (2)	2 (4)	4%
↓Phos	8 (15)	2 (4)	5 (20)	5 (10)	4 (8)	2 (4)	6 (12)	9%
↑Lactate	7 (13)	10 (19)	13 (25)	17 (33)	18 (35)	13 (25)	17 (33)	23%
↑Glucose	17 (33)	21 (40)	23 (44)	29 (56)	28 (54)	27 (52)	21 (40)	46%

↑High, ↓Low, Na: Sodium, K: Potassium, Mg: Magnesium, Phos: Phosphorus.

3.4. Factors associated with enteral nutrition provision and GI tolerance

Associations between clinical diagnosis and drug prescriptions with energy-protein deficits and GI intolerance during the first 7 days of EN were evaluated. In logistic regression models, only AKI diagnosis was associated with energy deficit at day 7 after adjusted covariates (adjusted OR 4.65, CI95% 1.19–18.1, p = 0.02). No associations for protein deficits and GI intolerance were observed (Table 5).

4. Discussion

This study is the first to describe the provision, safety, and tolerance of enteral nutrition in critically ill COVID-19 patients

Table 5
Associations between clinical diagnosis and drugs prescription with energy/protein deficits and GI intolerance.

Factors	Energy deficit day 7 (n = 29)		Protein deficit day 7 (n = 24)		GI Intolerance (n = 18)	
	OR (CI95%)	P value	OR (CI95%)	P value	OR (CI95%)	P value
AKI diagnosis	4.65 (1.19–18.1)	**0.02**	0.85 (0.26–2.8)	0.79	0.47 (0.12–1.72)	0.25
Diabetes mellitus	1.43 (0.43–4.7)	0.55	2.7 (0.8–9.0)	0.11	0.80 (0.23–2.8)	0.72
Hypertension	0.59 (0.18–1.91)	0.38	0.75 (0.23–2.4)	0.64	1.95 (0.56–6.7)	0.28
Benzodiazepines	1.9 (0.36–10.0)	0.44	0.62 (0.11–3.2)	0.57	1.23 (0.20–7.4)	0.82
NBA	1.45 (0.41–5.0)	0.558	1.24 (0.36–4.3)	0.73	0.62 (0.18–2.3)	0.47
Dexmedetomidine	0.63 (0.1–3.7)	0.61	0.16 (0.01–1.6)	0.12	4.3 (0.69–27.6)	0.12
Sedatives	0.61 (0.17–2.3)	0.47	1.57 (0.42–5.8)	0.49	0.54 (0.12–2.33)	0.40
Vasopressors	0.87 (0.2–3.8)	0.86	0.75 (0.17–3.2)	0.69	0.31 (0.06–1.6)	0.16
Steroids	0.37 (0.1–1.23)	0.10	0.39 (0.12–1.24)	0.11	0.70 (0.21–2.2)	0.55
GI symptom	0.65 (0.2–2.1)	0.48	1.25 (0.39–3.9)	0.70		
Lactate >2 mmol						
Day 1					1.94 (0.3–12.2)	0.48
Day 2					0.44 (0.08–2.1)	0.32
Day 3					0.58 (0.12–2.8)	0.50
Day 7					0.68 (0.13–3.5)	0.65

Adjusted to age and SOFA scale. AKI: acute kidney injury; NBA: neuromuscular blocking agents; GI: gastrointestinal; OR: odds ratio; CI95%: confidence interval 95%. Significant results p < 0.05 are in bold.

under mechanical ventilation. Gastrointestinal manifestations associated with COVID-19 might represent a problem to achieve energy and protein goals as they lead to enteral feeding interruptions. Consequently, these gastrointestinal alterations can cause inadequate energy provision, weight loss and decubitus ulcer development [17,18]. In our study, 90% of patients who received enteral nutrition achieved >80% of their goal requirements by day 7 (22.8 ± 7.3 kcal/kg), which helps to dismiss common clinical concerns regarding GI intolerance in these patients. The highest incidence of intolerance was observed on day 3 (13%), which can be explained by the fact that progression to reach goal requirements was made on this particular day. Whereas in day 7 we observed a 11% of intolerance overall. However, a global of gastrointestinal intolerance incidence observed in non-COVID19 ICU is around 26–50% [18–20]. Although this study only explored safety of EN in week one, the incidence of GI intolerance showed no association with the provision of EN.

In a multicentric study of 1321 critically ill patients, Zeinab Javid et al. report underfeeding (provision <80% of estimated nutritional requirements) in 79.5% of cases [20]. A similar prevalence was observed in another multicentric study of 3390 mechanically ventilated patients, where 74% failed to meet at least 80% of energy targets [21]. The inclusion of ICU dietitians could improve the adequacy of EN delivery [22]. In our sample, adequacy of energy at day 4 was 94.5% and 94.2% for protein provision, could be explained by the daily monitoring of gastrointestinal tolerance, considerations of non-nutritional calories from glucose/propofol infusions and individualization of enteral nutrition regimen.

Moreover, individualized prescription of EN is important to avoid overfeeding; a common syndrome associated with hyperglycaemia, hypercapnia with impaired ventilator weaning, hypertriglyceridemia, and increased insulin requirements [23]. Which is why energy amounts from non-nutritional sources should be factored into the nutrition prescriptions as done in this study where some patients received glucose and propofol infusions that provided high amounts of energy. On the contrary, underfeeding and malnutrition due to frequent EN interruptions in presence of GI dysfunction are common in critically ill patients [24]. In the ICU context, several factors might influence the presence of GI dysfunction like immobility, sedation, and hypoproteinemia [15]. Gastrointestinal integrity and functionality could be altered in patients with COVID-19, a suspicion raised due to symptoms such as diarrhea, anorexia, nausea, vomiting, and abdominal pain [13]. A meta-analysis on patients with COVID-19 reported a prevalence of 12.5% of diarrhea, 10.2% of nausea and vomiting, and abdominal discomfort in 9.2% [25]. While in the first week of EN, our study found a prevalence of 25% of gastroparesis, 11% of vomiting and diarrhea in 15% of the cases.

In this retrospective cohort, patients received some drugs that affect nutrient metabolism and gastrointestinal motility during the first week of hospital stay; 63% of patients received steroids, 73, 87 and 100% received NBA, benzodiazepines, and opioids, respectively. Drug regimen could be explaining the high prevalence of constipation observed (86.5%), as compared with previous reports with a prevalence between 24 and 84% in the regular ICU population [16,26]. This abnormality becomes relevant because of its impact on other outcomes such as nausea, vomiting, abdominal distention and, in rare cases, intestinal pseudo-obstruction that might cause perforation [26]. We observed no associations between prescribed medication or lactate concentrations higher than 2 mmol/L with the incidence of GI intolerance.

AKI is the most common complication associated with COVID19 in ICU [27]. In a multivariate regression model, only AKI diagnosis was associated with a higher caloric but not protein deficit. Our study also showed an association between AKI and higher energy deficit. Although interruption times during hemodialysis were not registered in this study, EN interruption due to hemodynamic instability during hemodialysis sessions, especially in patients that need higher doses of vasopressors during such treatment, might explain this deficit.

Our study is the first concerning GI intolerance and biochemical abnormalities associated to EN, providing evidence of EN as a safe intervention. The main strength of our study is the individualized prescription and monitoring of EN by an ICU dietitians' team. However, this study has some limitations; it was conducted at a single center that includes a small number of patients. Furthermore, the retrospective design was used in this study, and many patients were not included due to GI function missing data. Missing data was due to the lack of registration in the nursing chart of any of the gastrointestinal variables. Moreover, associations between GI symptoms and energy/protein deficits with infectious complications or patient outcomes were not evaluated.

In conclusion, EN is feasible and well-tolerated in COVID-19 critically ill patients receiving invasive mechanical ventilation in the first week of intubation. Clinical trials should be designed to explore the effect of nutritional interventions on infection course and clinical outcomes.

Statement of authorship

A. Osuna-Padilla, A. Aguilar-Vargas, and N. Rodriguez-Moguel equally contributed to the acquisition, analysis, and interpretation of the data; I. Osuna-Padilla and S. Rodriguez-Llamazares contributed to the analysis and interpretation of the data; and A. Osuna-Padilla, A. Aguilar-Vargas, and N. Rodriguez-Moguel contributed to the design of the research. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Declaration of competing interest

None declared.

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