ORIGINAL ARTICLE

GASTROINTESTINAL CHANGES IN CRITICAL PATIENTS WITH COVID-19 RECEIVING ENTERAL NUTRITIONAL, NEUROMUSCULAR BLOCKERS AND/OR VASOACTIVE DRUGS

Jessica Sayume Makiyama da Silva[1], Gabriela Lazzaron Slob[2], Danielle Dantas[3], Fernanda Furtado[4]
Jéssica Alves de Paula[5], Larissa Farinha Maffini[6], Luíza Silva Leite[7]
Sandra Regina Justino[8], Estela Iraci Rabito[9]

Highlights:

1. Constipation is the most frequent alteration among COVID-19 critically patients. 2. Higher doses of norepinephrine are associated with gastric residual volume (GRV).3. Increasing doses of fentanyl are associated with gastrointestinal alterations (GIA)

http://dx.doi.org/10.21527/2176-7114.2024.48.13615

How to cite:
da Silva JSM, Slob GL, Dantas D, Furtado F, de Paula JA, Maffini LF. et al. Gastrointestinal changes in critical patients with Vovid-19 receiving enteral nutritional, neuromuscular blockers and/or vasoactive drugs. Rev. Contexto & Saúde, 2024;24(48): e13615

[1] Universidade Federal do Paraná. Curitiba/PR, Brasil. https://orcid.org/0000-0003-1929-3723
[2] Universidade Federal do Paraná. Curitiba/PR, Brasil. https://orcid.org/0000-0001-6725-9242
[3] Universidade Federal do Paraná. Curitiba/PR, Brasil. https://orcid.org/0000-0002-6517-9684
[4] Universidade Federal do Paraná. Curitiba/PR, Brasil. https://orcid.org/0000-0003-1740-3159
[5] Universidade Federal do Paraná. Curitiba/PR, Brasil. https://orcid.org/0000-0001-5200-1783
[6] Universidade Federal do Paraná. Curitiba/PR, Brasil. https://orcid.org/0000-0001-9838-3617
[7] Universidade Federal do Paraná. Curitiba/PR, Brasil. https://orcid.org/0000-0003-4993-5678
[8] Universidade Federal do Paraná. Curitiba/PR, Brasil. https://orcid.org/0000-0002-2577-7751
[9] Universidade Federal do Paraná. Curitiba/PR, Brasil. https://orcid.org/0000-0002-3857-9746

ABSTRACT

Objective: The aim of this study was to evaluate the frequency of gastrointestinal alterations (GIA) and possible associated risk factors in critically ill patients with COVID-19 receiving enteral nutrition (EN) concomitantly with vasoactive drug (VAD) and/or neuromuscular blockers (NMB). **Methods:** Retrospective cohort study, performed in intensive care units (ICU), with individuals over 18 years of age with COVID-19 who received concomitant exclusive EN with at least one VAD and/or one NMB in ≥ 1 day. GIA were: presence of ≥ 1 of the following changes: diarrhea (≥ 3 liquid stools/day), gastric residual volume (GRV), paralysis of the lower gastrointestinal tract (GIT) (absent evacuation for ≥ 3 consecutive days), emesis and gastrointestinal bleeding. A mixed logistic regression was used to assess the association of drugs with GIA and a multivariate logistic regression to assess potential confounders. **Results:** We evaluated 78 individuals and 774 days of hospitalization. All of them received EN within 48h and 70.5% died. The most frequent GIA were: lower GIT paralysis, 75 patients in 362 days; GRV, 18 patients at 34 days and diarrhea, 13 patients at 22 days. Norepinephrine was associated with GRV (p=0.003) and fentanyl (mcg/min) with the presence of GIA (p=0.029). **Conclusions:** The NMB showed no relationship with the assessed GIA, as for the VAD we suggest the assessment of norepinephrine as a possible risk factor for GRV.

Keywords: Enteral Nutrition; Neuromuscular Blocking Agents; Vasoconstrictor Agents; COVID-19; Critical Care

ALTERAÇÕES GASTROINTESTINAIS EM PACIENTES CRÍTICOS COM COVID-19 RECEBENDO NUTRIÇÃO ENTERAL, BLOQUEADORES NEUROMUSCULARES E/OU DROGAS VASOATIVAS

RESUMO

Objetivo: avaliar a frequência de alterações gastrointestinais (AGI) e possíveis fatores de risco associados, em pacientes críticos com COVID-19 recebendo nutrição enteral (NE) concomitante com droga vasoativa (DVA) e/ou bloqueadores neuromusculares (BNM). **Metodologia:** Estudo de coorte retrospectivo, realizado em unidades de terapia intensiva

(UTI), com indivíduos maiores de 18 anos com COVID-19 que receberam NE exclusiva, concomitante, com no mínimo uma DVA e/ou um BNM em ≥ 1 dia. AGI foram: presença de ≥ 1 das seguintes alterações: diarreia (≥ 3 evacuações líquidas/dia), volume residual gástrico (VRG), paralisia de trato gastrointestinal (TGI) baixo (evacuação ausente por ≥ 3 dias consecutivos), êmese e sangramento gastrointestinal. Uma regressão logística mista com efeito aleatório foi utilizada para avaliar a associação das drogas com AGI e uma regressão logística multivariada para avaliar potenciais fatores de confusão. **Resultados:** Avaliamos 78 indivíduos e 774 dias de internamento. Todos receberam NE em até 48h e 70.5% morreram. As AGI mais frequentes foram: paralisia do TGI inferior, 75 pacientes em 362 dias; VRG, 18 pacientes em 34 dias e diarreia, 13 pacientes em 22 dias. A norepinefrina foi associada ao VRG (p=0.003) e o fentanil (mcg/min) à presença de AGI (p=0.029). **Conclusions:** Os BNM não demonstraram relação com as AGI avaliadas, quanto as DVA sugerimos a avaliação da norepinefrina como possível fator de risco para VRG.

Palavras-Chave: Nutrição Enteral; Bloqueadores neuromusculares; Vasoconstritores; COVID-19; Cuidados Críticos; Trato Gastrointestinal.

INTRODUCTION

The new coronavirus, first recognized in December 2019 in Wuhan, China, has already infected thousands of people around the world. Since then, several organizations, such as the World Health Organization, have published strategies for the prevention, treatment and recovery of coronavirus disease 2019 (COVID-19). About 5% of those infected need intensive care unit (ICU), and of these, 50% to 85% receive ventilatory support with neuromuscular blockers (NMB) and fluid resuscitation associated with the use of vasoactive drugs (VAD)[1,2].

It is recommended that enteral nutrition (EN) be started early, within 24 to 48 hours after admission to the ICU, as long as the setting of hemodynamic stability is present. Among the advantages of early feeding are: maintenance of intestinal integrity and reduction of unfavorable outcomes, such as infection and length of hospital stay[3–5].

Although the recommendation for early EN is unanimous among the guidelines[3–5], there are controversies when there is an association with VAD, because one of the responses to shock is the redistribution of blood flow in an attempt to maintain the perfusion of vital organs, which can lead to splanchnic vasoconstriction and increased risk of gastrointestinal disorders (GIA), such as non-occlusive mesenteric ischemia, which, despite being uncommon (0.3 to 3.8%), has a high mortality rate (approximately 80%)[6,7]. Currently guidelines do not establish safety limits for the use of EN concomitantly with the use of VAD, but authors draw attention to the fact that the use of VAD alone does not make EN impracticable[4,5,7].

Other drugs used in the treatment of patients with COVID-19 on mechanical ventilation are NMB, which by their actions at the neuromuscular junction blocking skeletal muscle contraction are used to reduce the patient's dyssynchrony with the ventilator, facilitating gas exchange and reducing the risk of barotrauma[8].

As for VAD, there are no recommendations on EN when using NMB, although its use is often related to GIA. When considering its site of action, NMB does not appear to be associated with reduced intestinal absorption or other signs and symptoms of GIA[8,9]. GIA during NMB therapy seem to be more associated with immobility, opioid use, fluid imbalance and underlying diseases[9].

In view of the possible adverse effects and/or controversies related to the administration of VAD and NMB and considering the lack of studies in patients with the severe form of COVID-19 that relate exposure to these drugs, in expressive amounts, for a prolonged time, and the possible interferences in the adequate supply of EN, the aim of this study was to evaluate the frequency of GIA and possible associated risk factors in critical patients with COVID-19 receiving EN using NMB and/or VAD.

METHODS

This is a retrospective cohort study, carried out in three ICUs of a tertiary public hospital in southern Brazil. This work was approved and the Free and Informed Consent Term was waived, in the cases of patients who died, by the Ethics Committee in Research on Human Beings of the Hospital Complex of Clinics of the Federal University of Paraná, n°4.284.467.

The study followed the criteria recommended by the publication "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE).

The sample was obtained for convenience, due to the unprecedented and recent nature of COVID-19 and, consequently, the impossibility of obtaining the mark and sample calculation. Data were collected from physical and electronic medical records and nutritional monitoring sheets until the end of hospitalization from May 2020 to February 2021.

Eligible for the study were ICU patients diagnosed with COVID-19, of both sexes, over 18 years of age, who received exclusive EN and, concomitantly, at least one VAD and/or one NMB on at least one day of treatment. Patients who received nutritional therapy by another route, exclusively or in a complementary way, during the entire hospitalization period or who had missing data were excluded.

Data collection included demographic data, Charlson comorbidity index[10], assessment of nutritional status using the Subjective Global Assessment tool (SGA)[11] and body mass index (BMI)[12,13]. Additionally, potential confounding factors for the development of GIA were collected and analyzed, such as use of prokinetics and antiemetics (metoclopramide, erythromycin and ondasetron), use of fentanyl, performance of the prone maneuver and outcome variables such as length of hospital stay and ICU and mortality.

Nutritional Therapy

The prescription of EN was made by ICUs dietitians according to the clinical condition of the patient and in line with the institutional protocol of nutritional therapy for critically ill patients infected with SARS-CoV-2 (elaborated according to current publications) and discussed daily with the unit's multidisciplinary team. Data recorded daily regarding EN included: time to start EN, formula energy density, infusion rate, energy and protein supply and adequacy (prescribed vs infused).

Height was estimated by knee height using an inelastic measuring tape[14,15]. For the calculation of nutritional needs (non-obese), the current weight measured was used, reported (by the patient or family through a call) or estimated by the arm circumference and knee height[16]. In the impossibility of obtaining the weight through the previous techniques, – in cases of edema and inability to mobilize - the ideal weight was used to calculate nutritional needs

according to BMI (mini-mum, average or maximum)[12,13]. For obese individuals, only the ideal weight (maximum BMI for age) was used. Adults with BMI >30kg/m²[12] and elderly people with BMI >27kg/m²[13] were considered overweight.

The nutritional offer was planned considering a gradual and individualized increase in EN, aiming at an energy goal of 15-20 kcal/kg/day in the first week, progressing to 25kcal/kg/day according to the patient's clinical condition[3,4]. In the rehabilitation phase, the goals were adjusted to 30kcal/kg/day[17], as long as there was no clinical contraindication. Non-nutritional energy (from propofol and intravenous solutions containing dextrose) was also accounted for in the nutritional prescription.

Protein was prescribed progressively, aiming for 1.3g/kg/day[5]. In the rehabilitation phase, the protein supply could reach 2.0-2.5g/kg/day[17]. For obese patients, the following recommendation was considered: BMI between 30-40 kg/m2 (2g/kg ideal weight) and BMI >40 kg/m2 (2.5g/Kg ideal weight)[3,4].

Vasoactive drug and neuromuscular blocker

VAD are medications that can be used in critically ill patients, typically in cases of vasodilatory shock, as they have peripheral, pulmonary, or cardiac vascular effects. They act in small doses with dose-dependent responses that are rapid and short-lasting, through receptors located in the vascular endothelium. Vasopressors are the most commonly used category of VADs in critically ill patients, with norepinephrine, vasopressin, and epinephrine being some of them[18].

While NMB agents induce relaxation of skeletal muscles by inhibiting the transmission of signals at the neuromuscular junction. These drugs are frequently employed in the ICU to optimize mechanical ventilation, facilitate endotracheal intubation and uppress shivering during therapeutic hypothermia following cardiac arrest. There are two types of NMB: depolarizing and non-depolarizing. The group of non-depolarizing NMBAs are the most used in the ICU and some examples are atracurium, cisatracurium, rocuronium, and vecuronium[19,20].

VAD and NMB data included drug type and dosage (mcg/min and mcg/kg/min) used during concomitant EN according to weight. For patients with ideal weight, the drug calculation

was performed only in mcg/min, while for those with actual weight, the drug calculation was performed both in mcg/min and mcg/kg/min.

Vasopressor dosages were converted into norepinephrine equivalents (NORE) according to the studies by Merchan *et al*., and Mancl and Muzevich[6,21]

Gastrointestinal changes

GIA were evaluated per day considering the infusion of different types of drugs during the overlap, the dose infused considering the time in minutes and the actual body weight (when available) of the corresponding individual. GIA was defined, following the definition proposed by Blaser *et al*, the presence of at least one of the following alterations[22]: diarrhea (≥ 3 liquid stools per day), gastric residual volume (GRV), lower gastrointestinal tract (GIT) paralysis (absence of defecation ≥ 3 consecutive days), emesis and gastrointestinal bleeding. The enteral tube was opened to measure the GRV only in the presence of abdominal distention and/or emesis.

Statistical analysis

Data were analyzed by R software (R Core Team, 2021). For descriptive analysis, the variables were tested for normality and the results are described in absolute and relative frequency (%), mean ± standard deviation (normal variables), and median and interquartile range (non-normal variables). Due to the dependence induced by the repeated measures structure (different patients followed for several days), a generalized linear mixed model (GLMM) was applied[23]. Initially, a mixed logistic regression with random effect was used to analyze the binary outcome, that is, the presence or absence of GIA. Then, to analyze the relationship between the drugs and each GIA in isolation, a mixed logistic regression with random effects was applied[24,25]. Due to the correlation/dependence of the NORE value with the dose of each vasoactive drug (norepinephrine, epinephrine and vasopressin), a separate logistic regression model was applied for this variable. A multivariate logistic regression was applied to verify possible confounding factors associated with GIA.

RESULTS

Initially, 173 patients were selected. The reasons for exclusion were, incomplete medical records or nutritional follow-up form during the review process (N = 48), age < 18 years (N = 1) and no days with exclusive EN concomitant with a VAD or NMB during ICU stay (N = 46). Therefore, a total of 78 patients and 774 days of hospitalization were evaluated. Information regarding sample characterization, nutritional therapy, drugs and outcomes are described in table 1.

Table 1: Sample characterization, nutritional therapy, drugs and outcomes.

Characteristics	Total = 78
Male, N (%)	45 (57.8)
Age, years[a]	62.5 (22 - 86)
Real body weight, kg, N = 57[b]	83.08 ± 20.3
BMI, kg/m², n = 64[b]	30.2 ± 7.18
SGA, n= 24	
Well nourished, N (%)	8 (33.3)
Moderately (or suspected) malnourished, N (%)	14 (58.3)
Malnourished, N (%)	2 (8.3)
CCI[c]	2 (1-3)
EFIR, ml/h[b]	39.4 ± 10.04
Non-nutritional energy, kcal/kg/d[c]	2.74 (1.4 - 4.6)
Total energy received, kcal/kg/d[c]	14.65 (8.7 - 17.5)
Received protein, g/kg/d[b]	0.77 ± 0.36
Norepinephrine, mcg/min, n = 631d[c]	8.06 (3.72 - 17.8)
Norepinephrine, mcg/kg/min, n =464d[c]	0.10 (0.04 - 0.2)
Epinephrine, mcg/min, n = 82d[c]	9.89 (2.67 - 16.4)
Epinephrine, mcg/kg/min, n = 60d[c]	0.13 (0.03 - 0.22)
Vasopressin, UI/min, n = 151d[c]	0.016 (0.01 - 0.02)
NORE, mcg/min, n = 710d[c]	8.9 (3.6 - 20.5)

NORE, mcg/kg/min, n = 526d[c]	0.12 (0.04 - 0.25)
Atracurium, mcg/min, n = 92d[c]	581.9 (416.6 - 805.5)
Atracurium, mcg/kg/min, n = 75d[c]	7.24 (5.55 - 8.51)
Cisatracurium, mcg/min, n = 18d[c]	1111.1 (648.1-1388.8)
Cisatracurium, mcg/kg/min, n = 18d[b]	10.1 ± 4.2
Rocuronium, mcg/min, n = 262d[c]	500.0 (305.5 - 666.7)
Rocuronium, mcg/kg/min, n = 187d[c]	6.25.12 (4.03 - 8.03)
Fentanyl, mcg/min, n= 630d[c]	83.3 (24.8 - 125)
Need for MV (%)	76 (97.43)
Length of hospital stay, d[c]	19.5 (13 - 26.2)
Length of ICU stay, d[c]	14.7 (9.1-19.2)
Hours to start EN[c],	19.6 (0* - 48)
Days on exclusive EN[c]	12 (8 - 19)
Deaths, n (%)	55 (70,5)

BMI, body mass index; CCI, Charlson Comorbidity Index; d, days; EFIR, enteral formula infusion rate; EN, enteral nutrition; ICU, intensive care unit; MV, mechanical ventilation; N, number of patients evaluated; NORE, norepinephrine equivalentes; SGA, Subjective Global Assessment. [a] median, minimum-maximum; [b] mean, standard deviation; [c] Median, interquartile range

* Patient using EN at the time of admission to the ICU.

The composition of the enteral nutritional products used was as follows: 58.9% were hypercaloric – 49.1% corresponded to a density of 1.5 kcal/ml - 57.4% were hyperproteic, 50.2% were isotonic, and 98.3% were fiber-free.

During the period evaluated, 97.4% (n = 76) of the sample presented at least one GIA. Lower GIT paralysis was the most frequent alteration, being observed in 75 patients (96.2%), followed by GRV and diarrhea (Table 2). On median, patients had 7 (4 - 9) GIA in 6.5 (4 - 9) days during ICU stay. The energy density of the offered formulas ranged from 1.0 to 2.0kcal/ml.

Table 2. Frequency of gastrointestinal changes on days on EN and therapy with at least one concomitant VAD and/or NMB.

Gastrointestinal changes	Patients (n=78) n (%)	Days (n = 774) n (%)
Diarrhea	13 (16.6)	22 (2.8)
GRV	18 (23)	34 (4.4)
Lower GIT paralysis	75 (96.1)	362 (46.8)
Emesis	4 (5.12)	9 (1.2)
Gastrointestinal bleeding	1 (1.28)	1 (0.1)

EN, enteral nutrition; GIT, gastrointestinal tract; GRV, gastric residual volume; NMB, neuromuscular blockers; VAD, vasoactive drug.

No changes in the composition of the enteral diet were observed in cases of gastrointestinal symptoms. However, a reduction in infusion rate was implemented in cases of persistent VRG and diarrhea.

The most used VAD and NMB were norepinephrine and rocuronium, being administered on 631 and 262 of the 774 days evaluated, respectively. The mixed logistic regression model did not show a significant association between the presence of VAD and NMB (Table 3) with the development of GIA. In the isolated assessment of the NORE dose (mcg/min) there was also no association with the presence of GIA (OR = 1.001; 95% CI 0.991 to 1.013; p = 0.803).

Table 3. Mixed logistic regression for association of gastrointestinal alterations, according to the presence of different VAD and NMB.

Drug	Estimate	SE	OR	CI 95%	*P*-value
Norepinephrine	0.125	0.291	1.134	0.637 to 2.002	0.666
Epinephrine	-0.100	0.379	0.905	0.429 to 1.907	0.792
Vasopressin	-0.359	0.202	0.699	0.469 to 1.037	0.075
Atracurium	0.108	0.261	1.114	0.664 to 1.861	0.681
Cisatracurium	0.743	0.540	2.102	0.751 to 6.481	0.169
Rocuronium	0.256	0.192	1.291	0.879 to 1.874	0.183

CI, confidence interval; NMB, neuromuscular blockers; OR, odds ratio; SE, standard error; VAD, vasoactive drug.

In the three most frequent GIA in our sample, the increase in drugs (mcg/min) was not related to lower GIT paralysis and diarrhea. However, an increase in norepinephrine (mcg/min) showed a significant association with the presence of GRV (Estimate = 0.816; EP = 0.272; p = 0.003). Due to the low frequency, it was not possible to perform the test for emesis and gastrointestinal bleeding.

In the multivariate analysis for possible confounders, prokinetic/antiemetic use, EN infusion rate, and prone position were not related to the development of GIA. The increase in fentanyl dose (mcg/min) was associated with the presence of the evaluated alterations (OR = 1,247; 95% CI 1,024 to 1,534; p = 0,029).

Finally, energy and protein adequacy did not differ between groups, being respectively 88.6% (64.6 - 99.6%) and 89.9% (69.2 - 100%) on the days with alterations and 89.4% (69.2 - 99.6%) and 90.8 % (74.4 - 100%) on days without. The increase in energy adequacy (OR = 1.219; 95% CI 0.879-1.787; p-value = 0.291) and protein (OR = 0.700; 95% CI 0.437-1.014; p = 0.118) were not related to the presence of GIA.

DISCUSSION

GIT paralysis was the most frequent alteration followed by GRV diarrhea among patients with COVID-19 admitted to the ICU. The assessment of the presence of different drugs did not impact the development of GIA. However, when evaluating the GIA individually, the highest dose of norepinephrine was associated with the presence of GRV, while increasing doses of fentanyl were associated with the recording of GIA.

GIT paralysis was more frequent than that observed in the studies by Prat *et al* (2016) (51.9%) and Nassar, Silva and Cleva (2009) (69.9%)[26,27]. Despite the high frequency, in our study there was no association between the use of VAD and NMB with GIT paralysis. Immobility, the use of opioids[28], such as fentanyl, used in 81.4% of the days evaluated and significantly associated with the presence of GIA, as well as hypoxemia may have contributed to the development of this alteration[28].

The μ-opioid receptors of the central nervous system that influence analgesia are also located in the GIT and through them opioid agonists decrease neuronal activity, acetylcholine secretion and impair GIT motility[26,28]. Prat *et al* (2016) evaluated 189 critically ill patients and found that the absence of evacuation for ≥ 6 days was associated with prolonged ICU stay and mechanical ventilation, showing how this GIA, sometimes neglected in clinical practice, can have great importance in patient outcomes.

In this work, the NORE calculation was used to assess the general need for vasopressors when different VADs were used concomitantly[21]. The received NORE showed no association with GIA, a result that corroborates previous findings that show benefits and safety of early EN in patients receiving 0.14 to 0.3mcg/kg/min of norepinephrine or NORE[6,7]**.**

A study evaluated 259 patients admitted to the ICU and found that doses ≤12.5mcg/min of NORE can be well tolerated[20]**.** This result makes it possible to consider the possibility of using VAD doses in decision-making aiming at greater safety in nutritional management, in view of the possible limitations for obtaining real body weight in this population. Norepinephrine may have been associated with GRV, when evaluated alone, due to the fact that a small part of our sample received values greater than what the literature has shown to be safe to avoid GIA, as evidenced by the interquartile range of 3.6 - 20.5mcg/ min of norepinephrine received.

Vasopressin and epinephrine were not associated with the development of GIA, although vasopressin is a VAD that acts directly on blood vessels and is associated with intestinal vasoconstriction and reduced gastric blood flow[7]. In our study, the dose received and the lower exposure to these drugs may explain the difference compared to previous results that showed an increase in GIA in the presence of these vasopressors and that suggested a greater risk of intestinal injury, due to the reduction of splanchnic and mesenteric blood flow[21].

The energy supply was lower than in previous studies[7,21], which may also have impacted on a lower ratio of GIA in the presence of EN concomitant with VAD. Osuna-Padilla *et al* evaluated 52 critically ill patients with COVID-19 on mechanical ventilation and concluded that EN is feasible and well tolerated in this population with a total energy infusion of 22.8 ± 7.3kcal/kg/day[29]. It is important to emphasize that the low energy and protein infusion found is probably associated with the clinical severity of the patients, with the need to start EN slowly and the need to reduce the supply due to clinical worsening followed by death, as observed by the high mortality rate found.

We did not find an association between the use of NMB and GIA, which corroborates previous studies that show little or no interference of the use of these drugs in the GIT[8,9,21]. Tamion *et al* (2013) evaluated the gastric emptying of 20 critically ill patients receiving cisatracurium and found that there was no increase in GRV at 1h and 2h after starting EN in the presence of the blocker.

Although studies suggest safety in the administration of EN while using NMB, it should be considered that pancuronium, vecuronium and rocuronium have vagal blockade as a side effect, whose site of action includes the GIT[8]. Autonomic dysfunctions, including vagus nerve disturbances and enteric nervous system abnormalities can affect gastric motility[30]. Therefore, we must be aware of possible GIA associated with NMB, until more robust studies are available.

In our research, all patients received early EN, as recommended by the main guidelines[3–5] and the mortality rate (70.5%) was similar to that observed in mechanically ventilated patients with COVID-19 from other public hospitals in Brazil (71.5%) in 2022[31]. Energy and protein adequacy were similar on days with and without GIA and improvement in EN adequacy was also not associated with its development. This result may reflect the presence of dietitians working daily at the bedside together with the multidisciplinary team of the ICUs.

In this study, fewer patients had real body weight, BMI and SGA compared to the total number of patients included, this was due to data collection difficulties, previously known in critically ill patients, such as obtaining anthropometric measurements, since these patients find bedridden and often sedated, with changes in volume and body composition resulting mainly from the acute phase of the disease, fluid replacement and the use of medications such as corticosteroids[32].

In addition, due to the workload imposed on health professionals in the midst of a pandemic period, added to the risk of exposure of family members and, consequently, the impossibility of allowing them to be present in the care process by providing information, also made it difficult to obtain this data. Given the difficulties reported, the responsible dietitian made telephone contact with the family members, aiming to reduce the impact of these obstacles in nutritional care.

Some limitations should be considered when interpreting and extrapolating our results to clinical practice. In this sense, we emphasize the need to consider the presence of GIA caused by other causes not investigated, we highlight: diabetes gastroparesis, diarrhea due to hypoalbuminemia or *Clostridium dificille*, increased lactate and severity of the disease, given its potential relationship with GIT malfunctions. Another limitation was that the time to defecate was evaluated since admission to the ICU and not since the last evacuation, therefore, despite the high prevalence, this data may still be underestimated.

We highlight some strengths of this work, such as: the daily assessment of VAD and NBM in COVID-19, whose best treatment is still unclear, requiring investigations. The total energy supply that has been thoroughly investigated, including non-nutritional sources.

CONCLUSION

In conclusion, in the evaluated sample, the NMB in the administered doses, in relation to the amount of EN received, did not show a relationship with the evaluated GIA. We suggest that EN be prescribed with caution during the duration and escalation of norepinephrine. Due to the novel character of the disease and its particularities, we suggest the development of larger, prospective and randomized studies for greater safety in the conduction of EN in association with VAD and NMB.

ACKNOWLEDGMENTS

The authors thank the COVIDNUT research team.

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Received: 26/09/2022

Accepted: 18/09/2023

Published: 22/02/2024

Authors' Contributions:

Jessica Sayume Makiyama da Silva: Conceptualization, Data curation, Formal analysis, Investigation, Project Administration, Validation, Visualization, Writing – original draft.

Gabriela Lazzaron Slob:Resources, Validation, Writing - review & editing.

Danielle Dantas: Resources.

Fernanda Furtado: Resources.

Jéssica Alves de Paula: Formal Analysis, Resources, Writing - review & editing.

Larissa Farinha Maffini: Resources.

Luíza Silva Leite:Formal Analysis, Resources, Writing - review & editing.
Sandra Regina Justino: Supervision, Writing - review & editing.
Estela Iraci Rabito: Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Writing - review & editing

All authors have approved the final version of the text.

Conflict of interest: There are no conflicts of interest.

Corresponding Author
Jessica Sayume Makiyama da Silva
Universidade Federal do Paraná
R. XV de Novembro, 1299 – Centro, Curitiba/PR, Brasil
jessicasayume@gmail.com

Editor: Dr. Giuseppe Potrick Stefani

Editor-in-chief: Dra. Adriane Cristina Bernat Kolankiewicz