Gastrointestinal and sensory manifestations, nutrition management, and energy-protein intake in hospitalized patients with COVID-19

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Abstract
Background: Gastrointestinal and sensory manifestations (GSMs) of coronavirus disease 2019 (COVID-19) may affect food intake, resulting in malnutrition and poor outcomes. We characterized the impact of GSMs and oral nutrition supplementation on energy-protein intake (EPI) and hospital discharge in adult patients with COVID-19.

Methods: Patients from two hospitals were enrolled (n = 357). We recorded the presence and type of GSM at admission, estimated energy requirements (EER) and the EPI based on regular food intake (plate diagram sheets) during hospital stays. Patients not achieving 60% of their EER from food over 2 consecutive days received oral nutrition supplementation (ONS) with a high-energy-protein oral drink.

Results: Most patients (63.6%) presented with GSMs at admission. Anorexia was the most common manifestation (44%). Patients with anorexia or more than one GSMs were more likely to not achieve 60% EER on the first day of follow-up and to require the ONS intervention (P ≤ 0.050). Prevalence of at least one GSM was higher in patients who did not achieve hospital discharge than in patients who achieved it (74.2% vs 54.6%, P = 0.038). The patients requiring ONS (26.9%) demonstrated good adherence to the intervention (79.3%), achieved their EER during 95.7% of the supplementation time, and presented with hospital discharge rates similar to patients not requiring ONS (92.2% vs 91.9%, respectively; P = 1.000).
CONCLUSIONS

GSM were prevalent in COVID-19 and it impaired EER attendance and patient recovery. ONS was well-tolerated, aided EER attendance, and potentially facilitated hospital discharge.

KEYWORDS

anorexia, COVID-19, gastrointestinal symptoms, nutrition therapy, oral nutrition supplement

INTRODUCTION

Beyond classic respiratory manifestations (CRMs), patients with the coronavirus disease 2019 (COVID-19) can also display extrapulmonary features. A retrospective multicenter study found that gastrointestinal disturbances were the most common complaint of patients with COVID-19 upon hospital admission (50.5%); these included anorexia, diarrhea, nausea/vomiting, and abdominal pain.1 The frequency of altered taste (dysgeusia) and smell (anosmia) ranged from 19.4% to 88.0%.2 Ubiquitous expression of the human functional receptor for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) across the gastrointestinal tract and the in-hospital use of antiviral medications might contribute to gastrointestinal manifestations.3 The pathogenic mechanism underlying smell and taste dysfunction has not yet been fully clarified; however, the former appears to involve the neurotropism and neuroinvasiveness of SARS-CoV-2.2,4 These extrapulmonary features seems to be prevalent and contribute to poor outcomes in COVID-19.5

Gastrointestinal and sensory manifestations (GSMs), amplified by the ventilatory and therapeutic support for COVID-19, may significantly impair oral food intake. Acute and persistent nonadherence in meeting energy-protein requirements (EPRs) together with the intense catabolism found in patients with COVID-19 can contribute to a fast acute malnutrition status associated with higher hospital morbidity and mortality.6-9 Available guidelines for nutrition care concerning patients with COVID-19 recommend, for those not achieving their EPRs with regular oral diet, to offer oral nutrition supplementation (ONS) with chemically defined nutrient content, along with dietary measures to improve appetite and prevent malnutrition.10,11

The present study is the first to evaluate the binomial GSMs and nutrition management on nutrition intake in patients with COVID-19. The prevalence of GSMs and the adherence in accepting ONS were assessed in hospitalized patients eating orally, along with their impact on energy-protein intake (EPI). These analyses were done considering patient hospital discharge.

MATERIAL AND METHODS

Study design and ethical issues

This prospective, multicenter, longitudinal, open clinical study was performed at two hospitals in São Paulo, Brazil, designated as local referral centers for the treatment of COVID-19: Hospital de Caridade São Vicente de Paulo (public) and Hospital Sírio-Libanés (private). The research protocol included two steps, as follows: step (1) observational step, focusing on GSM prevalence and step (2) interventional step, focusing on the adherence to a high-energy high-protein ONS. Both steps assessed its impact on EPI (primary end point) and hospital discharge (secondary end point). The protocol was registered at Plataforma Brazil (n° 34130820.4.1001.0068) and Brazilian Clinical Trials (https://ensaiosclinicos.gov.br/rg/RBR-3h5fr2s) and was approved by the local ethical committee (CAPPesq, n° 4.171.967). All patients or their legal representatives (when the patient was unable) provided written informed consent before inclusion. The flowchart of our study protocol is illustrated at the Supporting Information: Figure S1.

Patient selection

A convenience sample of 369 patients was recruited from the wards attended by the Multidisciplinary Nutrition Support Teams at both hospital centers. To address the observational step 1, we included adult patients (18–90 years old), both genders, any ethnicity, with COVID-19 suspected (lung imaging by computed tomography) or diagnosed (positive polymerase chain reaction). To address the interventional step 2, we included patients from the observational sample who ingested <60% of their EPN for 2 sequential days12 and did not present diabetes mellitus II with obligatory insulin use, dysphagia that prevented swallowing without thickener, supplemental enteral or parenteral nutrition therapy, previous use of a complete oral nutrition supplement, presence of three liquid bowel movements for 2 days, allergy or intolerance to any component of the oral nutrition supplement offered, bleeding, multiple dysfunctions of organs and systems, Sequential Organ Failure Assessment score >11.
points, Karnofsky Performance Scale <50%, previously current illness, and participation in another ongoing interventionist clinical study. Exclusion criteria for both observational and interventional samples were pregnancy, receiving palliative care, and absence of positive polymerase chain reaction for SARS-CoV-2 until the end of their hospital follow-up—meaning that all the patients included had proved diagnosis of COVID-19 disease.

**Descriptive data**

At study admission, which occurred within the first 48 h of patient admission to the COVID-19 treatment ward, we recorded age, sex, ethnicity, body mass index (BMI; usual weight/height²), underlying diseases, need for noninvasive respiratory support, presence of CRM (cough and dyspnea), and administered medications. Up to 36 h from admission, we also applied the nutrition risk screening 2002 tool (NRS-2002). Patients with NRS-2002 ≥ 3 were considered at nutrition risk.¹⁰,¹³

**Prevalence of GSMs (observational step)**

At study admission, patients were personally asked for the presence of diarrhea (>3 liquid evacuations per day), constipation (less than three evacuations per week), nausea/vomiting, lack of appetite after the first symptoms (anorexia), abdominal pain, disruption in the sense of taste (dysgeusia) and/or loss or impairment of sense of smell (anosmia). Prevalence of GSMs was characterized according to the following categories: at least one, more than one, and combined with respiratory symptoms. These categories were also used to assess the impact of GSMs on EPI and clinical outcome.

**Adherence to nutrition intervention (interventional step)**

For ONS, patients received the daily prescription of up to two units (125 ml per unit) of a complete high-energy-protein oral drink (Nutridrink Compact Protein⁶) with three flavors (vanilla, strawberry, and cappuccino), which was offered 2 h before or 2 h after the patient’s regular mealtime (preferentially to replace water during medication), for a maximum period of 25 days. The detailed oral nutrition drink composition is shown in Table 1. Adherence to the ONS was assessed by the daily recording of its intake and refusal. The ONS refusal was characterized by recording the patient’s complaints and clinical conditions, including intolerance to the oral nutrition drink taste and consistency, presence of any GSM, and any other sign and symptom of digestive intolerance. In the context of either severe gastrointestinal symptomatology or systematic refusal for 48 consecutive h, ONS was suspended, and the patient was continued to be evaluated only for GSM prevalence. The same procedure was applied when the calorie-protein supply from combined food and ONS intake remained below half the patient’s requirements for >1 week.¹⁰ Under these adverse conditions, the local medical team considered other nutrition support therapies (ie, enteral or parenteral).

**Compliance of EPI**

EPRs were estimated as follows: 20–25 kcal/kg for adult patients (18–64 years old); 30 kcal/kg for older adults (>65 years old), underweight patients or patients with multiple comorbidities; 27 kcal/kg for

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**TABLE 1** Main nutrition information of the complete oral supplement supplied to patients with coronavirus disease 2019 that did not achieve their energy-calorie needs up to 2 consecutive days during follow-up

| Component          | Amount per 100 ml (each bottle having 125 ml) |
|--------------------|-----------------------------------------------|
| Calorie density    | 2.4 Kcal/ml                                   |
| Calorie value      | 240 Kcal                                      |
| Calorie distribution | 24% protein, 40.7% carbohydrate, 35.3% fat |
| Carbohydrate       | 24 g                                          |
| Protein            | 14 g                                          |
| Total fat          | 9.4 g                                         |
| Saturated fat      | 0.9 g                                         |
| Trans fat          | 0 g                                           |
| ω-6 to ω-3 ratio   | 5:1                                           |
| Protein sources    | Casein (84%), potassium caseinate + sodium (16%) |
| Carbohydrate sources | Maltodextrin (50%), saccharose (49%), other (1%) |
| Fat sources        | Canola oil (56%), sunflower oil (44%)         |
| Fiber              | 0 g                                           |
| Osmolarity         | 570 mOsm/L                                    |

Note: Data provided by the manufacturer (Danone, Brazil).
patients >60 years of age with several comorbidities; 25 kcal/kg/day of ideal weight for patients who are obese; and 1.3 g/kg/day of protein for all patients, considering adjusted body weight for obese patients. At step 1, compliance with EPRs was estimated daily based on oral regular food intake using plate diagram sheets. For patients from the interventional step 2, compliance with EPRs also considered the amount of energy-protein acquired from ONS intake. Data on fasting and the type of diet offered (oral, enteral, or parenteral) were recorded.

Hospital discharge

Hospital discharge was recorded at the study end as the primary clinical outcome. Patients nonachieving hospital discharge included those admitted to ICU, palliative care, or dead.

Statistical analysis

Continuous variables were expressed using descriptive analysis to measure central tendency (mean or median) or measures of dispersion (SD or minimum-maximum). Categorical variables were expressed as means of percentage values in absolute and relative frequencies. The t test was performed to compare two continuous variables with a normal distribution (Anderson–Darling test). In contrast, the nonparametric Mann-Whitney and Brunner–Munzel tests were used for homogeneous and heterogeneous variables (Bartlett test), respectively. Fisher’s exact test was used for comparisons using categorical variables. Two-tailed hypotheses were evaluated, and the confidence intervals were 95%. To better explore our primary end point (EPI), we also performed multiple linear regression (MLR) analyses, accounting for potential confounders (comorbidities, gender, age, ventilation support, and severity) and using GSMs and ONS as the main explaining variables. Two approaches were applied for the MLR analyses having ONS as the main explaining variable: one considering the entire follow-up periods (before and during ONS) and the other considering only the supplementation period (during ONS). All statistical analyses were performed using Software R (version 4.0.2) and considering a significance level of 5%.

RESULTS

Flowchart of patient analysis

Of the 369 patients recruited, 12 were excluded because no COVID-19 diagnosis was confirmed by positive polymerase chain reaction until the end of the study. A total of 43 patients were not assessed for the impact of GSMs on EPI because they did not have complete dietary intake follow-up from study admission to their clinical outcome (n = 41) or needed enteral nutrition intervention (n = 2). A total of 96 patients were recruited to the interventional step by not achieving their EPRs over 2 consecutive days. All had complete dietary intake follow-up; however, nine refused to take ONS. Therefore, 87 patients were included in the interventional step 2. The CONSORT diagram illustrates the flowchart of all patients included in the study and their respective analyses (Figure 1).

Observational step 1: GSMs

Sample description

Detailed descriptive data from the 357 patients composing our observational step 1 are described in Table 2. They were predominantly male (57.1%), white (54.6%), with a median age of 60 (18–99) years and a median BMI of 28.3 (15.0–58.4) kg/m².

Prevalence of GSMs

Patients exhibited a high prevalence of GSMs (63.6%) that primarily included gastrointestinal symptoms, with 4.4% of individuals presenting only sensory manifestations (Table 2). The distribution according to the presence/absence of classical respiratory manifestations can be seen in Figure 2.

Impact of GSMs on EPI

Patients presenting with anorexia (P = 0.007) and more than one GSMs (P = 0.034) were more likely to not achieve 60% of their EPRs on the first day of study follow-up and to require ONS (Table 2). The frequency of at least one GSM was higher in patients needing ONS than in patients not requiring ONS (Table 2). In addition, our MLR analysis showed an inverse association between the presence of GSMs and EPI ($\beta = -6.90, P = 0.019$).
Impact of GSMs on hospital discharge

Three patients from the observational sample had unknown outcomes because they were transferred to another hospital. Prevalence of at least one GSM was higher in patients who did not achieve than in patients who achieved hospital discharge (74.2% vs 54.6%, $P = 0.038$).

Interventional step 2: ONS

Sample description

The 87 patients composing our interventional step 2 were predominantly male (52.9%) and white (47.1%), with a median age of 64 (18–99) years and a median BMI of 27.6 (14.5–51.6) kg/m². Compared with the group of patients not taking the ONS, they exhibited worse clinical markers, including a higher prevalence of more than one GSMs, risk of malnutrition, and need for noninvasive respiratory support and antiviral and antibiotic use (Table 2).

Adherence to ONS

For most patients from the interventional step 2 (74.7%), the ingestion of energy-protein from oral regular food under 60% of EPRs occurred at the earliest 2 days of follow-up. During the ONS supply, only 20.7% of them refused ONS partially or completely for at least 1 day during the entire intervention. There was a total of 43 refusals with a median time of 2.0 (1.0–3.0) days for the refusal to occur. Refusals were less common in patients with anosmia (11.1% vs 39.1% without anosmia; $P = 0.027$) and did not affect the overall nutrition supplementation once the median days of prescribed and received ONS supplementation were similar (4.0 [1.0–23.0] days vs 4.0 [0.0–21.0] days, respectively). Reasons given by patients for ONS refusal were flavor intolerance (30%), abdominal distension (16%), dislike (7%), dysphagia (2%), low appetite (5%), depression (5%), early satiety (2%), and liquid stools evacuation (2%). We were able to know a reason of some patients not to adhere to ONS because they presented with mental confusion (5%) or they simply refused to justify (26%).
# TABLE 2  Descriptive data of the patients with coronavirus disease 2019 studied

| Variable         | Description | Sample Without + with ONS, observational, n = 357 (%) | Sample Without ONS, n = 270 (%) | Sample With ONS, interventional, n = 87 (%) | P value |
|------------------|-------------|------------------------------------------------------|---------------------------------|---------------------------------|---------|
| Race             | Black       | 58 (16.5)                                            | 38 (14.3)                       | 20 (23.0)                       | 0.143   |
|                  | White       | 192 (54.6)                                           | 151 (57.0)                      | 41 (47.1)                       |         |
|                  | Asian       | 2 (0.6)                                              | 1 (0.4)                         | 1 (1.2)                         |         |
|                  | Pardo\(^a\) | 100 (28.4)                                           | 75 (28.3)                       | 25 (28.7)                       |         |
| Comorbidities    | Type 2 diabetes | 111 (31.1)                  | 86 (32.0)                       | 25 (28.7)                       | 0.597   |
|                  | Obesity     | 98 (27.5)                                            | 72 (26.7)                       | 26 (29.9)                       | 0.582   |
|                  | Hypertension | 143 (40.1)                                           | 108 (40.0)                      | 35 (40.2)                       | 1.000   |
|                  | Cancer      | 22 (6.2)                                             | 15 (5.6)                        | 7 (8.1)                         | 0.443   |
|                  | CVD         | 61 (17.1)                                            | 46 (17.0)                       | 15 (17.2)                       | 1.000   |
|                  | Lung disease | 38 (10.6)                                            | 31 (11.5)                       | 7 (8.1)                         | 0.429   |
|                  | Other\(^b\) | 39 (10.9)                                            | 33 (12.2)                       | 6 (6.9)                         | 0.235   |
| CRM              | Dyspnea     | 231 (64.7)                                           | 165 (61.1)                      | 66 (75.9)                       | 0.014   |
|                  | Cough       | 243 (68.1)                                           | 185 (68.5)                      | 58 (66.7)                       | 0.792   |
| GSM              | At least 1  | 227 (63.6)                                           | 159 (58.89)                     | 68 (78.16)                      | 0.001   |
|                  | Only one    | 75 (21.0)                                            | 53 (19.6)                       | 22 (25.3)                       | 0.290   |
|                  | >1          | 151 (42.3)                                           | 105 (38.9)                      | 46 (52.87)                      | 0.025   |
|                  | Diarrhea    | 75 (21)                                              | 56 (20.7)                       | 19 (21.8)                       | 0.880   |
|                  | Constipation | 41 (11.5)                                           | 26 (9.6)                        | 15 (17.2)                       | 0.080   |
|                  | Nausea/vomiting | 93 (26.1)                    | 67 (24.8)                       | 26 (29.9)                       | 0.399   |
|                  | Dysgeusia   | 92 (25.8)                                            | 67 (24.8)                       | 25 (28.7)                       | 0.483   |
|                  | Anosmia     | 103 (28.9)                                           | 74 (27.4)                       | 29 (33.3)                       | 0.341   |
|                  | Abdominal pain | 23 (6.4)                                           | 16 (5.9)                        | 7 (8.1)                         | 0.460   |
|                  | Anorexia    | 157 (44.0)                                           | 105 (38.9)                      | 52 (59.8)                       | 0.001   |
|                  | Combined with CRM | 201 (56.3)                        | 139 (51.5)                      | 62 (71.3)                       | 0.001   |
| Medication       | Antibiotic | 279 (78.2)                                           | 203 (75.2)                      | 76 (87.4)                       | 0.017   |
|                  | Antiviral   | 46 (12.9)                                            | 28 (10.4)                       | 18 (20.7)                       | 0.017   |
|                  | Anticoagulant | 317 (88.8)                                       | 241 (89.3)                      | 76 (87.4)                       | 0.696   |
|                  | Corticoids  | 288 (80.7)                                           | 216 (80.0)                      | 72 (82.8)                       | 0.641   |
|                  | Antiemetic  | 100 (28.0)                                           | 70 (25.9)                       | 30 (34.5)                       | 0.132   |
|                  | Antacids    | 62 (17.4)                                            | 43 (15.9)                       | 19 (21.8)                       | 0.254   |
| Nutritional risk | NRS-2002 ≥ 3 | 148 (41.6)                                           | 93 (34.6)                       | 55 (63.2)                       | <0.001  |
|                  | NIRS Required | 225 (63.0)                                       | 161 (59.6)                      | 64 (73.6)                       | 0.021   |
| Outcome          | Hospital discharge | 326 (91.3)                     | 247 (92.2)                      | 79 (90.8)                       | 1.000   |

Note: Data are expressed as the number (%) of patients, except for length of hospital stay, expressed in days. P value was generated by the Fisher-exact test (without ONS vs with ONS). Significant differences are highlighted in bold.

Abbreviations: CRM, classic respiratory symptom; CVD, cardiovascular disease; NRS-2002 ≥ 3, presence of nutritional risk; ONS, oral nutrition supplementation.

\(^a\)Pardo is a local nomination to describe a descendent from a mixture of races. We did not have Indigenous people in our sample.

\(^b\)Human immunodeficiency virus/acquired immunodeficiency syndrome, type 1 diabetes, and kidney, liver, and gut diseases.
Impact of ONS on EPI

There was a significant improvement in the EPI from regular diet combined with ONS than from regular diet alone (64.74 ± 13.22 vs 54.64 ± 10.98; \( P < 0.001 \)). Moreover, the intake from oral regular diet met \( \geq 60\% \) of EPRs only during 69.6\% of the ONS period; however, when adding the EPI from the ONS, the EPR fulfillment was 95.7\%. In addition, our MLR analysis displayed a significant inverse association between the need for ONS supplementation and EPI only before the intervention (\( \beta = -8.94 \), \( P = 0.002 \)).

Impact of ONS on clinical outcome

One patient from the interventional step 2 had an unknown outcome because he was transferred to another hospital. The frequency of hospital discharge was similar in patients needing and taking ONS and those not needing ONS (91.9\% vs 92.2\%, respectively, \( P = 1.000 \)).

DISCUSSION

Extrapulmonary symptoms may potentially predict poor outcomes in patients with COVID-19.\(^1\)\(^{16} \) We found that 60.8\% of patients with COVID-19 presented at least one gastrointestinal manifestation (independent of sensory manifestations) at study admission. Our findings conflict with systematic reviews and meta-analyses focusing on general symptoms of hospitalized patients with COVID-19, which reported a frequency of pooled gastrointestinal manifestations ranging from 10.1\% to 17.6\%.\(^{17-20} \) On the other hand, by focusing on gastrointestinal manifestations, Pan et al.\(^1 \) in China and Chen et al. in the United States\(^21 \) also found a comparatively higher frequency of gastrointestinal manifestations (50.5\% and 74.0\%, respectively). The prevalence of gastrointestinal manifestations appears to be higher outside of China.\(^22 \) For example, diarrhea and nausea/vomiting prevalence inside vs outside China was 7.7\% vs 18\% and 7.8\% vs 14.9\%, respectively.\(^{23,24} \) It appears that the study design and its origin may influence gastrointestinal manifestations measurement in patients with COVID-19, suggesting a higher prevalence worldwide than previously estimated.

The most common gastrointestinal symptoms reported in COVID-19 include diarrhea, nausea/vomiting, and anorexia, not necessarily in this order. Some clinical trials report a high prevalence of anorexia and diarrhea, including the one of Chen et al., who reported a 53\% and 50\% prevalence, respectively, of these gastrointestinal manifestations in 101 hospitalized patients with COVID-19.\(^21 \) In the present study, anorexia was the most prevalent gastrointestinal symptom (44\%). Furthermore, patients with anorexia were more likely to not achieve 60\% of their nutrition needs on the first day of study follow-up and further require the ONS intervention.

Changes in smell (anosmia) and taste (dysgeusia) were also reported in patients with COVID-19. Klein et al. found that hospitalized patients with COVID-19 experienced smell and taste changes between 3.9 and 4.6 days after disease onset, respectively\(^25 \); these manifestations were the longest-lasting symptoms, such that at the 6-month follow-up, 15\% and 8\%, respectively, still complained of smell and taste changes. In our study, 25.8\% had anosmia, and 28.9\% had dysgeusia at admission. However, only 4.4\% of our patients experienced these sensory manifestations in the absence of gastrointestinal symptoms. A total of 99 (77.9\%) patients experiencing dysgeusia or anosmia (\( n = 127 \)) presented with anorexia (data not shown). Our findings suggest that disrupted senses of smell and taste may contribute to gastrointestinal manifestations, primarily anorexia.
In our study, GSMs impaired EPI in the following manner: (1) failure to achieve 60% EPRs on the first day of follow-up was prevalent in patients with more than one GSM and patients with anorexia; (2) at last one GSM was observed in 78.2% patients requiring ONS; and (3) presence of GSMs showed a significant inverse association with EPI. Low energy-calorie intake predisposes patients to malnutrition, which is recognized as a risk factor for poor viral pneumonia outcomes. Accordingly, only 54.6% of our patients experiencing GSMs combined with respiratory manifestations achieved hospital discharge, in contrast to the 83.1% presenting only CRMs. Moreover, the prevalence of at least one GSM was higher in patients who did not achieve than in those who achieved hospital discharge. It appears that GSMs may contribute to more severe phenotypes of COVID-19, perhaps by impairing EPI.

In our study, 26.9% of patients with COVID-19 required ONS by not achieving 60% of their EPRs for 2 consecutive days, and 74.7% of them at the first 2 days of follow-up. An early energetic deficit was recently associated with a higher risk of death in invasive care–ventilated patients with COVID-19. Accordingly, our patients requiring ONS exhibited worse clinical markers (eg, higher nutrition risk) and higher GSM prevalence than patients who did not require ONS.

Adherence to the ONS intervention was high and quite efficient in aiding patients to achieve their EPRs because (1) significantly increased the amount of energy-protein ingested and (2) ensured EPR attendance during almost the entire intervention period. Even in clinically worse status, patients with energy-protein deficits nutritionally treated with ONS had a similar frequency of hospital discharge than those who did not require nutritional intervention. Our observations shed some light on the potential of oral nutrition supplementation to help patients with COVID-19 recover from their disease.

Our study is not free of limitations. Achievement of EPRs was based on food intake using plate diagram sheets. This method has been considered efficient for this purpose in large observational studies but may be imprecise in shorter samples. However, in practical aspects, the plate diagram sheets constituted the most suitable method for our team to overcome the unprecedent situation of restrictions for full patient access imposed by the COVID-19 pandemic. Strengths of our study include the prospective collection of data on GSMs (most studies in the area used retrospective data from medical and electronic records) and the assessment of a population that was representative of the general population in terms of number, gender, ethnicity, and socioeconomic status (recruited from public and private hospital centers).

**CONCLUSIONS**

Our findings highlight a high GSM prevalence in patients with COVID-19 that impaired energy-protein consumption and probably patient recovery. On the other hand, GSMs appear not to impair adherence to complete ONS, which was well-tolerated and helped patients achieve their EPRs and potentially recover from the disease. Oral nutrition supplementation appears to be a tool that prevents energy-protein malnutrition and its adverse consequences in the context of COVID-19.

**AUTHOR CONTRIBUTIONS**

Dan Linetzky Waitzberg, Paulo César Ribeiro, and Maria Carolina Gonçalves Dias equally contributed to the conception and design of the research; Raquel Susana Torrinhas and Yassmin Syagha contributed to the design of the research; Raquel Susana Torrinhas, Yassmin Syagha, Anna Carolina Pompermayer Coradelli, Bianca Zanchetta Buani Miguel, Thaís Nunes Freire, Marli Alves Ramelho da Silva, Fabiana Ruotolo, Daniela Hummel de Almeida, Janayna Nayara Buzato, Henrique Oliveira e Silva, and Ana Cristina Martinez contributed to the acquisition and analysis of the data; Raquel Susana Torrinhas, Dan Linetzky Waitzberg, and Paulo César Ribeiro contributed to the interpretation of the data; Raquel Susana Torrinhas and Dan Linetzky Waitzberg drafted the manuscript. All authors 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.

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**CONFLICT OF INTEREST**

This study was supported by Danone Nutricia (Brazil), which is the manufacturer of the oral supplement offered for part of the patients included in its protocol. The authors declare that Danone Nutricia (Brazil) did not interfere in the study design, collection, analysis, or interpretation of data, nor in the manuscript draft or the decision to submit this for publication. Together with
the statisticians, the authors were the only ones who had full access to all the data of this study, and they take complete responsibility for the data integrity and the accuracy of its analysis. The authors do not have any personal relationship with Danone Nutricia or other conflicts of interest to declare.

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REFERENCES
1. Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. *Am J Gastroenterol*. 2020;115:766-773.

2. Vaira LA, Salzano G, Fois AG, Piombino P, De Riu G. Potential pathogenesis of ageusia and anosmia in COVID-19 patients. *Int Forum Allergy Rhinol*. 2020;10:1103-1104.

3. Vespa E, Pugliese N, Colapietro F, Aghemo A. Stay (GI) healthy: COVID-19 and gastrointestinal manifestations. *Tech Innov Gastroint Endosc*. 2021;23:179-189.

4. Xydakis MS, Dehgan-Mobaraki P, Holbrook EH, et al. Smell and taste dysfunction in patients with COVID-19. *Lancet Infect Dis*. 2020;20:1015-1016.

5. Wei XS, Wang X, Niu YR, et al. Diarrhea is associated with prolonged symptoms and viral carriage in corona virus disease 2019. *Clin Gastroenterol Hepatol*. 2020;18:1753-1759.

6. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. *N Engl J Med*. 2014;370:1227-1236.

7. Dvir D, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. *Clin Nutr*. 2006;25:37-44.

8. Villet S, Chioler RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr*. 2005;24:502-509.

9. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. Association between malnutrition and clinical outcomes in the intensive care unit: a systematic review. *JPEN J Parenter Enter Nutr*. 2017;41:744-758.

10. Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr*. 2020;39:1631-1638.

11. Martindale R, Patel JJ, Taylor B, Arabi YM, Warren M, McClave SA. Nutrition therapy in critically ill patients with coronavirus disease 2019. *JPEN J Parenter Enteral Nutr*. 2020;44:1174-1184.

12. Campos LF, Barreto PA, Ceniccola GD, et al. Parcer BRASPEN/AMIB para o Enfrentamento do COVID-19 em Pacientes Hospitalizados. *BRASPEN J*. 2020;35:3-5. [in portuguese].

13. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. Educational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN). ESPEN guidelines for nutrition screening 2002. *Clin Nutr*. 2003;22:415-421.

14. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019;38:48-79.

15. Bjornsdottr I, Oskarsdottir ES, Thordardottir FR, Ramel A, Thordsdottir I, Gunnarsdottir I. Validation of a plate diagram sheet for estimation of energy and protein intake in hospitalized patients. *Clin Nutr*. 2013;32:746-751.

16. Noble YR, Phipps M, Zucker J, et al. Gastrointestinal symptoms and coronavirus disease 2019: a case-control study from the United States. *Gastroenterology*. 2020;159:373-375.

17. Silva FAFD, Brito BB, Santos MLC, et al. COVID-19 gastrointestinal manifestations: a systematic review. *Rev Soc Bras Med Trop*. 2020;53:e2000714.

18. Suresh Kumar VC, Mukherjee S, Harne PS, et al. Novelty in the gut: a systematic review and meta-analysis of the gastrointestinal manifestations of COVID-19. *BMJ Open Gastroenterol*. 2020;7:e000417.

19. Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2020;5:667-678.

20. Cheung KS, Hung IFN, Chan PPy, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. *Gastroenterology*. 2020;159:81-95.

21. Chen A, Agarwal A, Ravindran N, To C, Zhang T, Thuluvath PJ. Are gastrointestinal symptoms specific for coronavirus 2019 infection? A prospective case-control study from the United States. *Gastroenterology*. 2020;159:1161-1163.

22. Bilal M, Sawhney MS, Feuerstein JD. Coronavirus disease-2019: implications for the gastroenterologist. *Curr Opin Gastroenterol*. 2021;37:23-29.

23. Parasa S, Desai M, Thogulruva Chandrasekar V, et al. Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3:e2011335.

24. Sultan S, Altayar O, Siddique SM, et al. AGA Institute. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, metaanalysis of international data, and recommendations for the consultative management of patients with COVID-19. *Gastroenterology*. 2020;159:320-334.

25. Klein H, Asseo K, Karni N, et al. Onset, duration and unresolved symptoms, including smell and taste changes, in mild COVID-19 infections. A cohort study in Israeli patients. *Clin Microbiol Infect*. 2021;27:769-774.

26. Short KR, Kedzierska K, van de Sandt CE. Back to the future: lessons learned from the 1918 influenza pandemic. *Front Cell Infect Microbiol*. 2018;3:343.

27. Cereda E, Guzzardella A, Klersy C, et al. Early caloric deficit is associated with a higher risk of death in invasive ventilated COVID-19 patients. *Clin Nutr*. Published online March 2, 2021;S061-5614(21)00094-7. doi:10.1016/j.clnu.2021.02.020
28. Schindler K, Pernicka E, Laviano A, et al. How nutritional risk is assessed and managed in European hospitals: a survey of 21,007 patients findings from the 2007-2008 cross-sectional nutrition day survey. *Clin Nutr.* 2010;29:552-559.

**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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