Covid-19

# Nutritional intake and gastro-intestinal symptoms in critically ill COVID-19 patients

P.L.M. Lakenman [a, *], J.C. van Schie [a], B. van der Hoven [b], S.J. Baart [c], R.D. Eveleens [d], J. van Bommel [b], J.F. Olieman [a], K.F.M. Joosten [e]

[a] *Division of Dietetics, Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands*
[b] *Department of Intensive Care Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands*
[c] *Department of Biostatistics and Epidemiology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands*
[d] *Department of Anaesthesiology, Amsterdam UMC, Amsterdam, the Netherlands*
[e] *Intensive Care Unit, Department of Paediatrics and Paediatric Surgery, Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam, the Netherlands*

## ARTICLE INFO

## SUMMARY

*Background & aims:* Critically ill COVID-19 patients seem hypermetabolic and difficult to feed enterally, due to gastro-intestinal (GI) symptoms such as high gastric residual volumes (GRV) and diarrhea. Our aim was to describe the association of nutritional intake and GI symptoms during first 14 days of ICU admission.

*Methods:* Observational study including critically ill adult COVID-19 patients. Data on nutritional intake [enteral nutrition (EN) or parenteral nutrition] and GI symptoms were collected during 14 days after ICU admission. Target energy and protein feeding goals were calculated conform ESPEN guidelines. GI symptoms included GRV (ml/d), vomiting, abdominal distension, and faeces (ml/d). High GRV's were classified as $\geq 2$ times $\geq 150$ ml/d and diarrhea as Bristol stool chart $\geq 6$. GI symptoms were defined as mild if at least one symptom occurred and as moderate when $\geq 2$ symptoms occurred. Acute gastrointestinal injury (AGI) grades of III were classified as GI dysfunction and grades of IV were considered as GI failure with severe impact on distant organs. Linear mixed model analysis was performed to explore the development of nutritional intake and GI symptoms over time at day (D) 0, 4, 10, and 14.

*Results:* One hundred and fifty patients were included [75% male; median age 64 years (IQR 54–70)]. BMI upon admission was 28 kg/m$^2$ (IQR 25–33), of which 43% obese (BMI > 30 kg/m$^2$). Most patients received EN during admission (98% D4; 96% D10-14). Mean energy goals increased from 87% at D4 to 93% D10-14 and protein goals (g/kg) were increasingly achieved during admission (84% D4; 93% D10-14). Presence of moderate GI symptoms decreased (10% D0; 6% D4-10; 5% D14), reversely mild GI symptoms increased. Occurrence of GI dysfunction fluctuated (1% D0; 18% D4; 12% D10; 8% D14) and none of patients developed grade IV GI failure. Development of high GRV fluctuated (5% D0; 23% D4; 14% D10; 8% D14) and occurrence of diarrhea slightly increased during admission (5% D0; 22% D4; 25% D10; 27% D14). Linear mixed models showed only an association between AGI grades III and lower protein intake at day 10 (p = 0.020).

*Conclusion:* Occurrence of GI symptoms was limited and seems no major barrier for EN in our group of critically COVID-19 patients. Nutritional intake was just below requirements during the first 14 days of ICU admission. The effect on nutritional status remains to be studied.

## 1. Introduction

The coronavirus disease 2019 (COVID-19) is caused by the virus SARS-CoV-2 and can result in respiratory and gastro-intestinal (GI) complaints [1,2]. Approximately 20–30% of the hospitalized COVID-19 patients are being admitted to the intensive care unit (ICU) for respiratory and/or hemodynamic support [1,3]. In these

\* Corresponding author. Erasmus Medical Centre, Dr. M olewaterplein 40, 3015 GD, Rotterdam, the Netherlands.
*E-mail address:* p.lakenman@erasmusmc.nl (P.L.M. Lakenman).

patients, the median ICU stay ranges from 5 to 19 days [4] (see Fig. 1).

Initiating enteral nutrition (EN) within the first 24−48 h after ICU admission is recommended when patients are unable to eat [5,6]. Feeding critically ill patients is challenging due to several reasons such as GI dysfunction and mechanical problems (e.g., gastric tube occlusion or malposition) [7−9]. Optimal feeding goals are often not achieved [10,11], which can lead to a prolonged ICU stay and increased (infectious) complications [12]. Critically ill patients admitted with COVID-19 seem particularly hypermetabolic [13−15] and difficult to feed enterally, due to feeding intolerance resulting in high gastric residual volumes (GRV) and diarrhea [16,17]. Concerning feeding intolerance, different definitions for adult critically ill patients are used but there is no uniform definition [9]. Most commonly used definitions include the presence of GI symptoms such as diarrhea, bowel distension, vomiting, and absence of bowel sounds [18]. It is stated that in a conceptional framework for defining feeding intolerance in critically ill patients assessment of gastropareses and diarrhea have to be included [19]. GRV volumes over 300 ml (2x > 150 ml in preceding 24 h) are indicative of delayed gastric emptying [20], whereas faeces volumes over 350 g are likely to indicate malabsorption [21]. Due to a lack of clinical evidence a classification for feeding intolerance has been proposed based upon expert opinion. The proposed classification for acute gastrointestinal injury (AGI) ranges from grade I (Risk of developing GI dysfunction or failure) up to grade IV (GI failure with severe impact on distant organ function) [22].

Recently, AGI grades III and IV were observed in 50% of critically ill COVID-19 patients and were associated with a higher risk of prolonged mechanical ventilation and mortality [23,24]. Furthermore, in these patients, feeding intolerance based on clinical symptoms was frequently observed [16,23,25] and associated with poor clinical outcomes [16]. So far only one retrospective study in which 52 patients were included described the safety and GI tolerance of EN during the first week of ICU admission in critically ill COVID-19 patients [26]. Therefore, our aim was to further examine the association between EN and GI symptoms in a larger group of patients and beyond the first week up to first 14 days of ICU admission. We hypothesized that GI symptoms influenced achievement of adequate nutritional intake.

## 2. Material and methods

### 2.1. Study population and design

This observational study was conducted from April 2020 till November 2020 in the ICU of the Erasmus Medical Centre (MC), with the approval from the institutional review board of the Erasmus MC, Rotterdam, The Netherlands (MEC-2020-0336). The need for informed consent was waived by the Institutional review board. Conform our previous study [15], all adult patients (>18 years) admitted to the ICU with confirmed COVID-19 respiratory infection were included. Patients with a metabolic disease requiring a specific diet (e.g., Phenylketonuria) or (home)-parenteral nutrition (PN) starting >7 days before admission unrelated to COVID-19, were excluded.

### 2.2. Data collection

From the patient data management system (HiX™, Chipsoft, Amsterdam, The Netherlands) data were collected. Patient's baseline characteristics included age, weight, height, sex, body mass index (BMI), mortality risk score (APACHE-IV), and comorbidities. Additional variables were collected at day (D) 0, 4, 10, and 14 and included body temperature, illness severity score (SOFA-score), gradation of sedation depth (RASS-score), plasma inflammatory markers (C-reactive protein (CRP), interleukin-6 (IL-6), use of medication (prokinetics and laxatives) and opiates (sufentanil, remifentanil), type of mechanical ventilation, GI function (AGI grades), and nutritional data (enteral or parenteral intake, type of feeding tube, caloric and protein intake, non-nutritional calories, calculated- and prescribed feeding goal).

#### 2.2.1. Nutritional intake

Daily recorded nutritional intake included administered nutritional energy (kcal) and protein (g) and non-nutritional calories (e.g., propofol and glucose) intake per day during the first 14 days of admission. The initial goal was to increase nutritional intake gradually conform ESPEN guidelines [6,27,28]. Optimal feeding goals were determined individually per time point at D0, D4, D10, and D14 after admission by ICU dietitians [6]. The calculated nutritional goal (CNG) for energy corresponds with the estimated
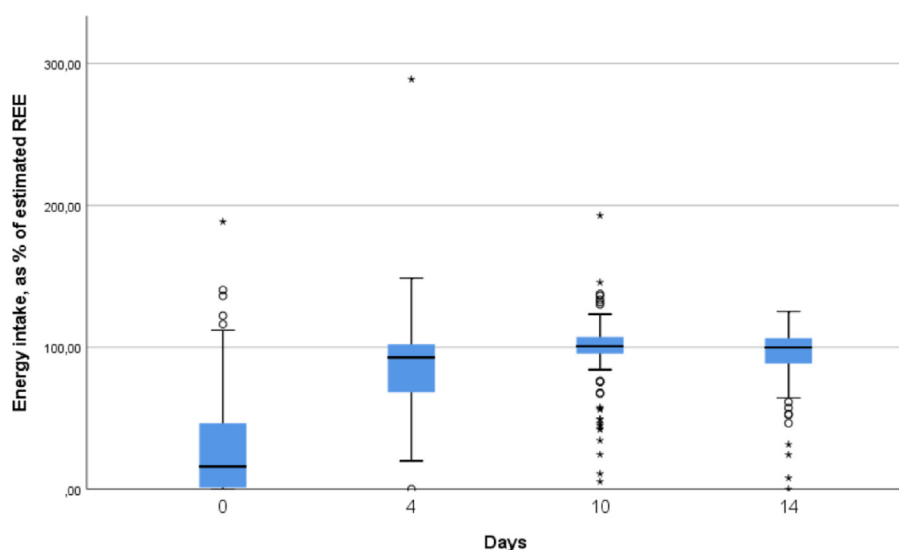


**Fig. 1.** Boxplot of the daily energy intake (% goal) of critically ill COVID-19 patients during the first 14 days of ICU admission. Available measurements decreased during admission (150 patients D0, 140 patients D4, 104 patients D10, and 82 patients D14).

total energy requirement. Resting energy expenditure (REE) was measured with an indirect calorimeter (Q-NRG+, Cosmed, Italy) conform the practical guidelines [29], unless contra-indications were present (e.g., hemodynamic instability, FiO2 > 70%) [30]. In case of contra-indications predictive formulas such as the WHO (BMI ≤ 30 kg/m$^2$) or Harris and Benedict (BMI > 30 kg/m$^2$) equation were used [31–33]. Correction of energy goal for influential factors were made individually and ranged from 0 to 30%. The CNG for protein generally ranges from 1.3 to 1.7 g/kg [5,6], taking into account the presence of wounds and continue renal replacement therapy [5,6]. Actual bodyweight (kg) upon admission was used to determine CNG, unless there was clinical manifestation of fluid overload, estimated usual bodyweight before admission was used [15]. The total delivered nutritional intake was calculated by adding all calories and grams of protein from EN, enteral liquid protein modules, PN, and non-nutritional sources.

### 2.2.2. Gastro-intestinal symptoms

Data of GI symptoms were collected at D0, D4, D10, and D14 after ICU admission. GI symptoms included GRV (ml/d), vomiting (y/n), abdominal distension (y/n), and faeces (ml/d). High GRV was defined as ≥2 times ≥150 ml/d conform our standard feeding protocol [5,6,20]. Diarrhea was defined as Bristol stool scale ≥6 [34]. GI symptoms were defined as mild if at least one symptom occurred and as moderate when ≥2 symptoms occurred. AGI grades of III were classified as GI dysfunction and grades of IV were considered as GI failure (with severe impact on distant organs) [19,22].

### 2.3. Route of feeding

EN was started 24–48 h after admission via nasogastric tubes, unless contraindications were present (e.g., haemodynamic instability). Generally polymeric high-protein formulas were administrated continuously [35], if necessary supplemented with enteral liquid protein modules. In case of high GRV, there was a low-threshold switch to placement of nasoduodenal tubes. If EN was not (fully) tolerated, the use of (supplemental) PN was weighted case-by-case [6].

### 2.4. Statistical analysis

Data on baseline characteristics were analyzed by means of descriptive statistics: mean (SD), median [interquartile range (IQR)] and numbers [percentages (%)]. Development of nutritional intake over time was presented in figures. Linear mixed model analysis was performed to explore the development of nutritional intake and GI symptoms over time. With mixed models all available information of patients during the study period is used. Multivariable analyses were conducted with daily nutritional intake, as % of estimated REE, as a dependent variable (i.e., energy and protein intake). Four analyses were performed with four different independent variables: the single dichotomous GI symptoms (i.e., diarrhea and high GRV), the sum score of GI symptoms (i.e., moderate GI symptoms), and GI dysfunction (i.e., AGI grades > II). When a single variable occurred in less than 5% of the patients it was excluded for analysis because of limited information in this risk factor. Time was included as a continuous fixed effect. Associations were expected to differ per time point. Therefore, additional models were estimated with time as a factor and an interaction with the four different independent variables to obtain associations on the specific days. All models were adjusted for age, gender, BMI, comorbidities, SOFA score, and CRP, no variable selection procedures were used. To account for repeated measurements random intercepts were included in the models. Due to the linear mixed

model analysis, no imputation was performed on missing data in the repeated measurements. The baseline characteristics were observed in all patients. Assumptions for linearity and normality of residuals were checked before interpretation of the results. Correction for multiple testing was performed. Data analysis was performed using IBM SPSS statistics for windows, version 25.0 (IBM Corp. Armonk, NY, USA). A two-sided p-value of less than $\alpha = 0.05$ was considered to be statistically significant.

## 3. Results

### 3.1. Study population

A total of 150 patients critically ill COVID-19 were followed during the first 14 days of admission. The number of patients decreased over time, due to discharge from the ICU or death. As presented in Table 1, median age was 64 years (IQR 54–77) and 75% of the patients were male. Median BMI upon admission was 28 kg/m$^2$ (IQR 25–33), of which 43% was obese (BMI>30 kg/m$^2$). One-third of the patients had at least one comorbidity, in which diabetes mellitus type 2 (32%), cardiac (32%)- and respiratory disease (21%) were the most prevalent. Minority of patients (8%) had pre-existing GI comorbidities (e.g., inflammatory bowel disease, gastrectomy, reflux oesophagitis). Most patients (71%) were transferred from other ICUs to the ICU in the Erasmus MC, with a median of 3 days (IQR 0–4) spend in another ICU.

A total of 38 patients (25%) died during ICU admission. Median ICU stay was 19 days (IQR 12–32) and surviving patients were ventilated for 18 days (IQR 10–30). Overall median length of hospital stay was 23 days (IQR 14–35).

### 3.2. Nutritional intake and route of feeding

Majority of the patients received EN during admission (98% D4; 96% D10-14). Less than 10% of the patients received (S)PN (2% D4; 6% D10; 9% D14). Nasogastric tubes were used more often in the first 4 days (74%) as opposed to D10 and D14 (55%). High-protein-polymeric formulas were mainly used during admission (99% D4; 97% D10-14). Supplementation of liquid enteral protein modules was used in 35% of the patients at D4, 55% at D10 and 60% at D14. Mean delivery of prescribed calorie goals increased from 87% at D4 to 93% D10-14 (Fig. 1). Protein goals were increasingly achieved during admission (84% D4; 93% D10-14) (Fig. 2). Most patients received >80% of the energy- (66% D4; 83% D10-D14) and protein goals (55% D4; 80% D10-D14).

**Table 1**
Baseline characteristics of the 150 included critically ill COVID-19 patients at ICU admission.

|  | N = 150 |
|---|---|
| Male sex, n (%) | 113 (75) |
| Age (years), median (IQR) | 64 (54.0–77.0) |
| BMI (kg/m$^2$), median (IQR) | 28.4 (25.3–32.5) |
| Underweight, n (%) | 1 (1) |
| Normal weight, n (%) | 32 (21) |
| Overweight, n (%) | 52 (35) |
| Obese, n (%) | 65 (43) |
| APACHE IV score, median (IQR) | 24.9 (1.7–31.9) |
| Comorbidities, n (%) |  |
| 1 comorbidity | 50 (33) |
| ≥2 comorbidities | 39 (26) |
| Transferred from another ICU, n (%) | 106 (71) |

APACHE IV, Acute Physiology and Chronic Health Evaluation IV; BMI, body mass index; ICU, intensive care unit.
APACHE IV is expressed as a score, where a higher score indicates higher risk on mortality at admission.
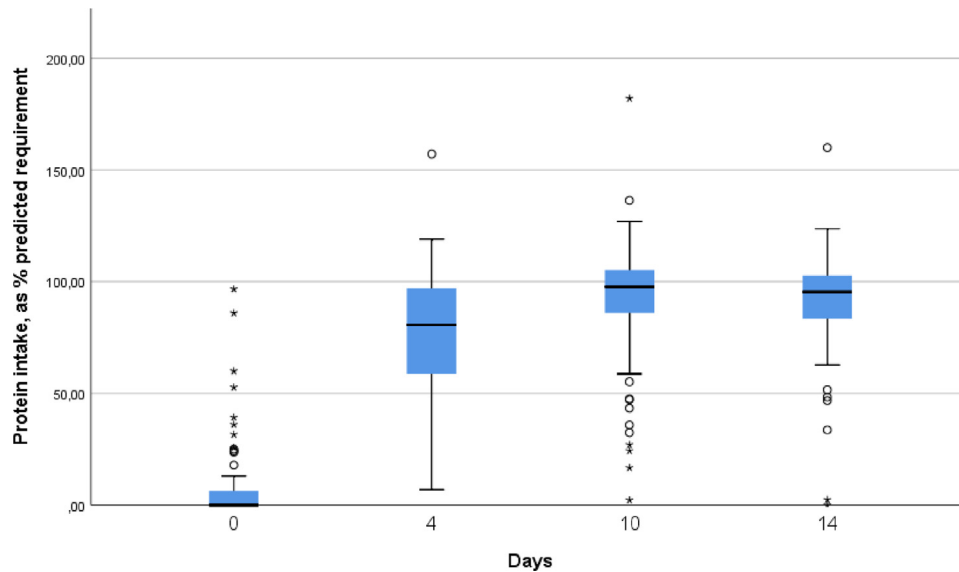
**Fig. 2.** Boxplot of the daily protein intake (% of goal) of critically ill COVID-19 patients during the first 14 days of ICU admission. Available measurements decreased during admission (150 patients D0, 140 patients D4, 104 patients D10, and 82 patients D14). ICU, intensive care unit; REE, resting energy expenditure.

### 3.3. GI symptoms

Presence of moderate GI symptoms decreased; reversely mild GI symptoms increased during admission (Table 2). None of patients developed AGI grades IV. High GRV was highest at D4 and there-after decreased. Diarrhea was seen in approximately a quarter of the patients at D4, 10, and 14. Overall vomiting and abdominal distention occurred in less than 5% of the patients. Use of laxatives remained respectively 75% during the first 10 days, reduced to 55% at D14. Prokinetics increased from 15% at D0 to 39% at D14.

### 3.4. Nutritional intake versus GI symptoms in the first 14 days

Linear mixed model analyses showed no significant association between diarrhea, high GRV, and AGI III and nutritional intake over time, as presented in Table 3. Moderate GI symptoms were associated with higher energy intake (p = 0.008). Fourteen percent of the patients with high GRV received liquid enteral protein modules, compared to 86% in patients with low GRV. Even though in patients with high GRV who did not receive enteral liquid protein modules, the protein intake increased during admission (80% D4; 90% D10-14). Overall no difference for nutritional intake and GI symptoms was found between obese and nonobese patients, data not shown.

### 3.5. Nutritional intake versus GI symptoms per time point

Table 4 presents the associations between GI symptoms and nutritional intake per timepoint, after adjustments. At D0 moderate GI symptoms was significantly associated with higher energy intake (p = 0.020) and diarrhea was significantly associated with higher energy- (p = 0.039) and protein intake (p < 0.001). There-after these associations disappeared. AGI grades > II were significantly associated with lower protein intake on D10 (p = 0.020). Overall, no significant associations were found at D14.

### 4. Discussion

This study emphasizes the possibility of adequate enteral feeding in critically ill COVID-19 patients with acceptable GI intolerance during the first 14 days of admission. Most patients could be fed enterally and nutritional intake was just below estimated goals during ICU admission. Moderate GI symptoms occurred in the minority of the patients on different time points (<10%) and none of the patients developed GI failure (AGI grade IV). Overall, patients presenting with moderate GI symptoms were associated with higher energy intake during admission. Furthermore, we found an association between AGI grades III and lower protein intake at D10.

**Table 2**
Presence of GI symptoms in critically ill COVID-19 patients during the first 14 days of ICU admission.

| Type | Day 0 (N = 150) | Day 4 (N = 140) | Day 10 (N = 104) | Day 14 (N = 82) |
|---|---|---|---|---|
| Diarrhea[a], n (%) | 8 (5,5) | 31 (22) | 26 (25) | 22 (27) |
| High GRV[b], n (%) | 8 (5,5) | 32 (23) | 15 (15) | 7 (5,8) |
| Vomiting, n (%) | 2 (1,5) | 5 (4) | 2 (2) | 3 (4) |
| Abdominal distention, n (%) | 3 (2) | 7 (5) | 3 (3) | 3 (4) |
| Moderate GI symptoms[c], n (%) | 15 (10) | 9 (5,6) | 7 (7) | 4 (5) |
| AGI score, n (%) | | | | |
| Grade I | 122 (81) | 43 (31) | 50 (48) | 47 (58) |
| Grade II | 26 (18) | 72 (51) | 42 (40) | 28 (34) |
| Grade III | 2 (1) | 25 (18) | 12 (12) | 7 (8) |
| Grade IV | 0 | 0 | 0 | 0 |

AGI, Acute Gastrointestinal Injury; GI, gastro-intestinal; GRV, gastric residual volume; ICU, intensive care unit.
[a] Diarrhea defined as Bristol stool chart ≥6.
[b] High GRV defined as ≥2 times ≥150 ml p/d.
[c] Moderate GI symptoms defined as ≥2 symptoms occurred.

**Table 3**
Multivariable associations between GI symptoms[c] and nutritional intake in critically ill COVID-19 patients over time during first 14 days of ICU admission, presented separately for energy and protein intake (% calculated nutritional goal).

|  |  | Coefficient[a] | 95% CI | p-Value[d] |
|---|---|---|---|---|
| Energy intake | Diarrhea[b] | 5.7% | −11.4; 22.8% | 0.512 |
|  | High GRV[b] | 7.6% | −8.5; 23.7% | 0.700 |
|  | Moderate GI symptoms[b] | 42.7% | 16.5; 68.9% | **0.008** |
|  | AGI score > II[b] | 9.1% | −5.2; 23.3% | 0.627 |
| Protein intake | Diarrhea[b] | 7.2% | −7.6;-22.1% | 1.000 |
|  | High GRV[b] | −7.3% | −21.9; 7.2% | 1.000 |
|  | Moderate GI symptoms[b] | 9.0% | −17.3; 35.2% | 0.499 |
|  | AGI score > II[b] | −6.1% | −19.0; 6.8% | 0.692 |

AGI, acute gastrointestinal injury; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; GI, gastro-intestinal, GRV, gastric residual volume; SOFA, sequential organ failure assessment.
Bold values in this table are considered significant (p < 0.05).
  [a] Exponent of the coefficients quantifies the increase or decrease in the average of the main outcome.
  [b] Adjusted for age, gender, BMI (kg/m$^2$), comorbidities(y/n), SOFA score, and CRP (mg/l).
  [c] Since vomiting and abdominal distention occurred in <5% of the patients, they were not taken into account.
  [d] P-values were corrected for multiple testing.

**Table 4**
Multivariable associations between GI symptoms[c] and nutritional intake in critically ill COVID-19 patients at D0, 4, 10, 14 during ICU admission, presented separately for energy and protein intake (% calculated nutritional goal).

|  |  | Coefficient[a] | 95% CI | p-Value[d] |
|---|---|---|---|---|
| Energy intake | **Day 0** |  |  |  |
|  | Diarrhea[b] | 72.1% | 15.7; 128.4% | **0.039** |
|  | High GRV[b] | 24.6% | −16.5; 65.7% | 0.317 |
|  | Moderate GI symptoms[b] | 75.8% | 24.2; 127.5% | **0.020** |
|  | AGI score > II[b] | 17.9% | −16.4; 52.4% | 0.302 |
|  | **Day 4** |  |  |  |
|  | Diarrhea[b] | 15.1% | −9.7; 39.4% | 0.458 |
|  | High GRV[b] | −13.8% | −34.4; 6.9% | 0.567 |
|  | Moderate GI symptoms[b] | 39.8% | −9.2; 70.5% | 0.660 |
|  | AGI score > II[b] | −3.1% | −23.4; 17.2% | 0.761 |
|  | **Day 10** |  |  |  |
|  | Diarrhea[b] | 6.7% | −16.2; 29.6% | 1.000 |
|  | High GRV[b] | −11.2% | −37.9; 5.4% | 1.000 |
|  | Moderate GI symptoms[b] | 1.8% | −52.3; 55.9% | 0.946 |
|  | AGI score > II[b] | −12.8% | −35.4; 9.7% | 1.000 |
|  | **Day 14** |  |  |  |
|  | Diarrhea[b] | −8.0% | −35.6; 19.5% | 1.000 |
|  | High GRV[b] | 21.2% | −13.6; 56.1% | 0.916 |
|  | Moderate GI symptoms[b] | 24.6% | −27.9; 77.2% | 1.000 |
|  | AGI score > II[b] | 6.9% | −20.8; 34.6% | 0.622 |
| Protein intake | **Day 0** |  |  |  |
|  | Diarrhea[b] | 137.4% | 90.6; 184.3% | **<0.001** |
|  | High GRV[b] | −11.7% | −66.8; 43.5% | 1.000 |
|  | Moderate GI symptoms[b] | −6.2% | −47.7l 46.5% | 0.979 |
|  | AGI score > II[b] | 1.8% | −43.4; 47.1% | 1.000 |
|  | **Day 4** |  |  |  |
|  | Diarrhea[b] | 18.5% | −1.6; 38.6% | 0.142 |
|  | High GRV[b] | −20.3% | −36.9;-3.7% | 0.068 |
|  | Moderate GI symptoms[b] | 8.9% | −18.7; 36.7% | 0.519 |
|  | AGI score > II[b] | −16.1% | −31.8; −0.4% | 0.132 |
|  | **Day 10** |  |  |  |
|  | Diarrhea[b] | 11.4% | −7.2; 30.1% | 0.452 |
|  | High GRV[b] | −22.9% | −44.3; −1.7% | 0.105 |
|  | Moderate GI symptoms[b] | −14.9% | −64.4; 34.5% | 0.547 |
|  | AGI score > II[b] | −25.3% | −42.9; −7.8% | **0.020** |
|  | **Day 14** |  |  |  |
|  | Diarrhea[b] | −5.7% | −28.2; 16.9% | 1.000 |
|  | High GRV[b] | 7.6% | −20.4; 35.6% | 1.000 |
|  | Moderate GI symptoms[b] | −0.6% | −47.7; 46.5% | 0.979 |
|  | AGI score > II[b] | −6.7% | −28.3; 14.9% | 1.000 |

AGI, acute gastrointestinal injury; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; GI, gastro-intestinal; GRV, gastric residual volume; SOFA, sequential organ failure assessment.
Bold values in this table are considered significant (p < 0.05).
  [a] Exponent of the coefficients quantifies the increase or decrease in the average of the main outcome.
  [b] Adjusted for age, gender, BMI (kg/m$^2$), comorbidities (y/n), SOFA score, and CRP (mg/l).
  [c] Since vomiting and abdominal distention occurred in <5% of the patients, they were not taken into account.
  [d] p-values were corrected for multiple testing.

Contrary to our hypothesis, GI symptoms had little influence on nutritional intake and vice versa. Both energy and protein intake were gradually increased during the observation period and mean delivery remained just below nutritional goals according to current guidelines (93% at D10-14). In our study around 80% of the patients received >80% of their nutritional goals during ICU stay. In those

patients who didn't reach these nutritional goals this might be explained by interruptions of feeding during medical procedures. This is in accordance with a recent study in which 90% COVID-19 patients received >80% of their nutritional needs with acceptable GI intolerance by D4 after ICU admission [25] and higher compared to a general ICU population in which it has been shown that 60–70% of the prescribed nutritional goals were delivered at D4 and D12 after admission [36]. This difference might be explained due to variations in disease course and its effect on nutritional support between a COVID-19 and a general non-COVID-19 ICU population.

Presence of moderate GI symptoms remained low in our study. Other studies in critically ill COVID-19 patients have used different definitions for feeding intolerance at different moments and therefore presence of reported feeding intolerance varies from 11 to 84% [16,23,26]. The liberal use of prokinetics and laxatives in our study could have decreased the presence of moderate GI symptoms. Comparison of results with non-COVID-ICU patients will be hampered by the heterogeneity of this population as several other factors might also influence GI symptoms (i.e., use of medication, opiates and pancreatic exocrine insufficiency) [19,21,37,38].

To harmonize the definitions for feeding intolerance an AGI classification has been proposed [22]. We found AGI grade III in 1–18% of the patients on the different time points and none of our patients developed grade IV (GI failure). This is line with a recent study in which none of the critically ill COVID-19 patients were diagnosed with AGI grade IV [39]. Other studies found higher percentages of GI dysfunction (AGI > II) in critically ill COVID-19 patients, 50–74% [23,24]. These higher percentages might be due to the subjective manner to classify AGI grades, which is a limitation of this classification system. In addition, medical policies and (GI) procedures per hospital may differ. Based on our results GI dysfunction seems no major issue in critically ill COVID-19 patients.

We observed an association between patients presenting with AGI grades III and lower protein intake at D10. Controversially, there was no association between these symptoms and energy intake. This might be explained by our caution in administrating enteral liquid protein modules in patients with AGI grades III. We recently observed a negative urinary protein balance in both the acute and the late phase of critically ill COVID-19 patients which might indicate a prolonged protein breakdown phase and the necessity to reconsider the need for a higher protein intake in this specific disease [15]. Based on these results it seems important to reassess the administration of enteral liquid protein modules to optimize protein intake in patients with AGI grades III.

Although we were able to feed our critically ill COVID-19 patients with acceptable GI symptoms conform our nutrition protocol, its effect on nutritional status and ICU-acquired weakness remains to be studied. It has been shown that muscle mass decreases rapidly during admission in critically ill patients due to the catabolic and immobilization state [40]. Future studies are recommended to assess nutritional intake in relation to body composition in COVID-19 patients during ICU admission and (long-term) follow-up after discharge from the hospital.

Some limitations of this study must be addressed. First, due to the observational study design all data concerning nutritional intake and GI symptoms/dysfunction were collected from medical charts and might be subject to underreporting. Second, the scope of this study was the first 14 days of ICU admission but provides no insights into the period afterwards. Taken into account the median length of ICU stay (9–15 days) of critically ill COVID-19 patients, a substantial part of ICU stay is included.

## 5. Conclusion

The occurrence of GI symptoms in our group of critically ill COVID-19 patients was low and seems no major barrier for providing EN. Nutritional intake was just below nutritional goals during ICU admission. It is recommended to monitor adequate protein intake in patients with more GI symptoms (AGI III). The effect on nutritional status and ICU-acquired weakness remains to be investigated.

## Funding

## Author contributions

All authors conceived and designed the research; PLL, BVH conducted the measurements and calculations; PLL, JCS, SJB analysed the data; PLL wrote the manuscript. All authors have read, edited and approved the manuscript.

## Conflict of interest

None declared.

## References

[1] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324(8):782–93.

[2] Mao R, Qiu Y, He J-S, Tan J-Y, Li X-H, Liang J, 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(7):667–78.

[3] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.

[4] Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, Pearson CAB, et al. COVID-19 length of hospital stay: a systematic review and data synthesis. BMC Med 2020;18(1):1–22.

[5] McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). J Parenter Enteral Nutr 2016;40(2):159–211.

[6] Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38(1):48–79.

[7] Engel JM, Mühling J, Junger A, Menges T, Kärcher B, Hempelmann G. Enteral nutrition practice in a surgical intensive care unit: what proportion of energy expenditure is delivered enterally? Clin Nutr 2003;22(2):187–92.

[8] Wang S, Ma L, Zhuang Y, Jiang B, Zhang X. Screening and risk factors of exocrine pancreatic insufficiency in critically ill adult patients receiving enteral nutrition. Crit Care 2013;17(4):R171.

[9] McClave SA, Gualdoni J, Nagengast A, Marsano LS, Bandy K, Martindale RG. Gastrointestinal dysfunction and feeding intolerance in critical illness: do we need an objective scoring system? Curr Gastroenterol Rep 2020;22(1):1–8.

[10] Ridley EJ, Peake SL, Jarvis M, Deane AM, Lange K, Davies AR, et al. Nutrition therapy in Australia and New Zealand intensive care units: an international comparison study. J Parenter Enteral Nutr 2018;42(8):1349–57.

[11] Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 2009;35(10):1728–37.

[12] Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med 2014;370(13):1227–36.

[13] Whittle J, Molinger J, MacLeod D, Haines K, Wischmeyer PE, Whittle J, et al. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. Crit Care 2020;24(1):581.

[14] Yu PJ, Cassiere H, DeRosa S, Bocchieri K, Yar S, Hartman A. Hypermetabolism and COVID-19. J Parenter Enteral Nutr 2020;44(7):1234–6.

[15] Lakenman PLM, van der Hoven B, Schuijs JM, Eveleens RD, van Bommel J, Olieman JF, et al. Energy expenditure and feeding practices and tolerance

during the acute and late phase of critically ill COVID-19 patients. Clin Nutr ESPEN 2021;43:383−9.

[16] Liu R, Paz M, Siraj L, Boyd T, Salamone S, Lite T-LV, et al. Feeding intolerance in critically ill patients with COVID-19. Clin Nutr 2021. S0261-5614(21)00180-1.

[17] Arkin N, Krishnan K, Chang MG, Bittner EA. Nutrition in critically ill patients with COVID-19: challenges and special considerations. Clin Nutr 2020;39(7): 2327.

[18] Blaser AR, Starkopf L, Deane AM, Poeze M, Starkopf J. Comparison of different definitions of feeding intolerance: a retrospective observational study. Clin Nutr 2015;34(5):956−61.

[19] Reintam Blaser A, Deane AM, Preiser JC, Arabi YM, Jakob SM. Enteral feeding intolerance: updates in definitions and pathophysiology. Nutr Clin Pract 2021;36(1):40−9.

[20] Kar P, Jones KL, Horowitz M, Chapman MJ, Deane AM. Measurement of gastric emptying in the critically ill. Clin Nutr 2015;34(4):557−64.

[21] Wierdsma NJ, Peters JHC, Weijs PJM, Keur MB, Girbes ARJ, van Bodegraven AA, et al. Malabsorption and nutritional balance in the ICU: fecal weight as a biomarker: a prospective observational pilot study. Crit Care 2011;15(6):R264.

[22] Blaser AR, Malbrain MLNG, Starkopf J, Fruhwald S, Jakob SM, De Waele J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med 2012;38(3):384−94.

[23] Drakos P, Volteas P, Cleri NA, Alkadaa LN, Asencio AA, Oganov A, et al. Acute gastrointestinal injury and feeding intolerance as prognostic factors in critically ill COVID-19 patients. J Gastrointest Surg 2021:1−10.

[24] Sun J-K, Zou L, Liu Y, Zhang W-H, Li J-J, Kan X-H, et al. Acute gastrointestinal injury in critically ill patients with coronavirus disease 2019 in Wuhan, China. World J Gastroenterol 2020;26(39):6087−97.

[25] Kaafarani HMA, El Moheb M, Hwabejire JO, Naar L, Christensen MA, Breen K, et al. Gastrointestinal complications in critically ill patients with COVID-19. Ann Surg 2020;272(2):e61.

[26] Osuna-Padilla I, Rodríguez-Moguel NC, Aguilar-Vargas A, Rodríguez-Llamazares S. Safety and tolerance of enteral nutrition in COVID-19 critically ill patients, a retrospective study. Clin Nutr ESPEN 2021;43:495−500.

[27] Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional

[28] Barazzoni R, Bischoff SC, Busetto L, Cederholm T, Chourdakis M, Cuerda C, et al. Nutritional management of individuals with obesity and COVID-19: ESPEN expert statements and practical guidance. Clin Nutr 2021. S0261−5614(21)00248-[X].

management of individuals with SARS-CoV-2 infection. Elsevier 2020;142(3−4):75−84.

[29] Singer P, Pichard C, De Waele E. Practical guidance for the use of indirect calorimetry during COVID 19 pandemic. Clin Nutr Exp 2020;33:18−23.

[30] Achamrah N, Delsoglio M, De Waele E, Berger MM, Pichard C. Indirect calorimetry: the 6 main issues. Clin Nutr 2021;40(1):4−14.

[31] Kruizenga HM, Hofsteenge GH, Weijs PJ. Predicting resting energy expenditure in underweight, normal weight, overweight, and obese adult hospital patients. Nutr Metab 2016;13:85.

[32] Roza AM, Shizgal HM. The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. Am J Clin Nutr 1984;40(1): 168−82.

[33] Human energy requirements: report of a joint FAO/WHO/UNU Expert Consultation. Food Nutr Bull 2005;26(1):166.

[34] Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. Gastroenterology 2016;150(6):1393−407.

[35] Thibault R, Seguin P, Tamion F, Pichard C, Singer P. Nutrition of the COVID-19 patient in the intensive care unit (ICU): a practical guidance. Crit Care 2020;24(1):1−8.

[36] Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical outcomes related to protein delivery in a critically ill population: a multicenter, multinational observation study. J Parenter Enteral Nutr 2016;40(1):45−51.

[37] Hay T, Bellomo R, Rechnitzer T, See E, Abdelhamid YA, Deane AM. Constipation, diarrhea, and prophylactic laxative bowel regimens in the critically ill: a systematic review and meta-analysis. J Crit Care 2019;52:242−50.

[38] Blaser AR, Deane AM, Fruhwald S. Diarrhoea in the critically ill. Curr Opin Crit Care 2015;21(2):142−53.

[39] Lin J, Guo F, Yin J. Nutritional practice in critically ill COVID-19 patients: a multicenter ambidirectional cohort study in Wuhan and Jingzhou. Asia Pac J Clin Nutr 2021;30(1):15−21.

[40] Preiser JC, Ichai C, Orban JC, Groeneveld ABJ. Metabolic response to the stress of critical illness. Br J Anaesth 2014;113(6):945−54.