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Original article

Diarrhoea and constipation during artificial nutrition in intensive care unit: A prospective observational study

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SUMMARY

Purpose: To describe the occurrence of gastrointestinal (GI) complications, specifically diarrhoea and constipation, in artificially (enterally or parenterally) fed critically ill patients within their first seven-day stay in Intensive Care Unit (ICU).

Methods: Observational prospective study conducted from September 1st to October 30th, 2019 and from August 1st to October 30th, 2021, in an ICU of a 1000-bed third-level hospital. General characteristics, nutritional variables, and medications administered were recorded and analysed. This study was registered on ClinicalTrials.gov (Identifier: NCT05473546).

Results: In total, 100 critically ill patients were included. Diarrhoea was present in 44 patients (44.0%), while constipation occurred in 22 (22.0%) patients. Patients with diarrhoea were generally those admitted for respiratory failure, whereas patients without diarrhoea were mostly affected by neurological disorders (22.7% vs 25%, respectively; $p = 0.002$). Likewise, patients with constipation were primarily those admitted for trauma (36.4%). Trauma patients were almost 24 times more likely to be constipated than patients with respiratory failure (OR 23.99, CI 1.38–418.0) and patients receiving diuretics were over 16 times more likely to have diarrhoea than patients not receiving diuretics (OR 16.25, IC 1.89–139.86).

Conclusion: GI complications of enteral nutrition represent still a very common issue in ICU. The main predictor of constipation was an admission for trauma whereas the main predictor of diarrhoea was the use of diuretics. Clinicians should consider and integrate these findings into more personalized nutritional and management protocols to avoid gastrointestinal complications.

1. Introduction

Nutrition in critically ill patients represents an important therapeutic tool whose importance is increasingly recognized [1].

According to the most recent guidelines [2], enteral nutrition (EN) should be preferred, unless contraindicated, over parenteral nutrition (PN). However, gastrointestinal (GI) dysfunctions are common in critically ill patients and could prevent full EN administration [3].

The pathophysiology of GI dysfunctions in critically ill patients is caused by a number of underlying mechanisms – often poorly understood – such as impaired bowel absorption, altered GI motility, changes in the microbiota, increased intra-abdominal pressure, reduced mesenteric perfusion, drug side effects, and GI tract infections [4]. As a consequence, the clinical effects (e.g.,

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feeding intolerance) may increase patient's morbidity and length of stay in Intensive Care Unit (ICU), exacerbating multi-organ failure, or further worsening to life-threatening conditions [5].

Gastrointestinal complications, particularly bowel movement disorders (i.e., diarrhoea and constipation), are the most frequent problems encountered in critically ill patients requiring EN [3]. A recent study including more than one thousand patients enrolled in 12 University and community ICUs in Canada, the United States, Poland, and Saudi Arabia [6] reported an incidence of diarrhoea of 73.8% (95% CI 71.1–76.6), with a high variability across centres.

On the other hand, the reported incidence of constipation in ICU ranges from 20 to 83% [7,8]. A large retrospective observational study, which was conducted by Yoshida et al. on almost two thousand adult patients in a general ICU in the period 2011–2018, found that the proportion of patients who were constipated decreased as the days passed (67% in the first 72 h and 36% after 144 h from ICU admission) [9]. Moreover, according to a retrospective observational study on 876 patients, ICU-stay was significantly longer in the late defecation group (12 vs 16 days, $p = 0.021$) [10].

The epidemiology of GI dysfunction in the critically ill is still limited in quality, partly related to heterogeneous patient populations and varying criteria and definitions of diarrhoea and constipation. Furthermore, few studies have investigated constipation and diarrhoea within the first week of ICU stay.

The aim of this study was to describe the occurrence of GI complications in a single-centre cohort of critically ill patients enterally fed within the first 7 days of ICU stay. Risk factors associated with diarrhoea and constipation were assessed.

2. Methods

2.1. Study design

This observational prospective study was approved by the Regional Ethics Committee of Friuli Venezia Giulia, Italy (CEUR-2019-Os-17), and was conducted according to the criteria set by the Declaration of Helsinki. Confidentiality was ensured by the investigators during each step of data handling. Written informed consents were obtained before enrolling patients.

The study was carried out at the Intensive Care Department of Academic Hospital of Udine, a 1000-bed third-level hospital in the north-east of Italy.

The study was retrospectively registered on ClinicalTrials.gov (Identifier: NCT05473546 registered on 26 July 2022).

All patients admitted to the general ICU from September 1st to October 30th, 2019 and from August 1st to October 30th, 2021 were evaluated for inclusion. Between the two study periods, no data were collected due to the lack of available research staff who was engaged in the ongoing COVID pandemic.

2.2. Setting and population

The ICU setting in our hospital is a conventional open space area with some separate rooms for special conditions (infective patients). Registered nurses (RNs), physicians, and Nursing Assistants (NAs) made up the personnel. Typically, our ICU has a critical care physician to patient ratio of 1:6 and a RN to patient ratio of 1:2 per shift.

The ICU sedation protocol in use, in compliance with each clinical situation, quickly allows having a lightly sedated or fully calm and awake patient, ranging from a −2 to 0 level according to the Richmond Sedation Agitation Scale (RASS). No restrictions are made regarding the type of sedatives to be used in the protocol; however, propofol, remifentanil, and dexmedetomidine are the selected drugs in over 90% of regimens.

Energy and caloric goals followed ESPEN guidelines [2], and, whenever possible, EN through nasogastric tube was preferred. At our Institution, we aim to reach these targets within 5 days by continuous infusion. No selective digestive decontamination is applied in our department.

Tests for *Clostridium difficile* and other common faecal pathogens are made only in case of diarrhoea lasting >2 days.

Inclusion criteria were: age ≥18 years old with an expected ICU-stay ≥72 h and need of artificial nutrition support. We excluded: patients with a pre-planned admission to the ICU as a consequence of elective major surgery; patients who did not require any nutritional support; those with a known gastrointestinal dysfunction (for example, gastrointestinal fistula, chronic diarrhoea or history of malabsorption); patients who tested positive for SARS-CoV2 infection (through PCR nasal swab analysis); those with a severe chronic renal disease (defined as estimated glomerular filtration rate <30 mL/min) or liver disease (diagnosed cirrhosis and/or patient in a waiting list for liver transplantation); lastly, those patients who refused to participate in our research and patients for whom end of life decision was made.

2.3. Data collection and study outcomes

The following patient information were collected: 1) general variables (age, gender, BMI [Body Mass Index], admission diagnosis, APACHE II [Acute Physiologic Assessment and Chronic Health Evaluation] score, SOFA [Sequential Organ Failure Assessment] score, mechanical ventilation, positive *C. difficile*); 2) nutritional variables at ICU admission (NUTRIC [Nutrition Risk in Critically ill] score, serum albumin, type of nutrition (EN or PN), dietary fiber administration, patients with interruptions to EN, vomiting episodes, GRV [Gastric Residual Volume] >300 mL [at least one event]); and 3) medications (=antibiotics, diuretics, enemas, vasopressors, insulin, laxatives, neuromuscular blocking agents, opioids (remifentanil, fentanyl, sufentanyl, morphine), non-opioids sedatives with continuous infusion for at least 24 h s [propofol, dexmedetomidine], and prokinetic agents).

Data were anonymously collected daily into a dedicated Microsoft Excel® sheet (v. 2019, Redmond, WA).

Data were reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statements to improve truthfulness and guarantee clarity [11].

2.4. Primary and secondary outcomes

The primary outcome was to establish the incidence of constipation and diarrhoea within the first 7 days as further specified. Diarrhoea was defined as the passage of three or more liquid stools per day [6] within 72 h from admission, whereas, according to a previous definition in literature [9], constipation is to be understood as no defecation within 7 days after the ICU admission.

The secondary outcome was to investigate whether any general-nutritional-medication variable could be associated with constipation or diarrhoea.

2.5. Sample size calculation

Considering an incidence of diarrhoea of 36% as reported by Ferrie & East (2007) [12] for a specified alpha error of 0.05 and a power of 0.90, 91 subjects were required. Supposing a 10% of drop out, we decided to include 100 patients for the final statistical analysis.

In order to be more inclusive, we chose to consider diarrhoea for sample size estimation since its incidence was reported to be lower than constipation, according to literature data [13].

2.6. Statistical analysis

Data were analysed using R software (The R Foundation) [14]. Continuous variables are reported as median (interquartile range [IQR]) and discrete parameters are reported as absolute value (percentage). According to the nature of the variables, differences between groups were assessed via T-test, Wilcoxon-test, Chi-squared test, and Fisher's exact test. The normality of the distribution was evaluated implementing the Shapiro–Wilk test.

Logistic regression models were performed to identify variables associated with constipation and diarrhoea. A decision to keep a variable as a predictor in the model was based on statistical ($p < 0.1$ in the univariate analysis) and clinical significance (for example, prokinetic agents).

A $p < 0.05$ was considered to be statistically significant. No imputation was done for missing data.

3. Results

One-hundred critically ill patients were included in this study after applying inclusion/exclusion criteria, as shown in the study flow chart in Fig. 1.

Patients' characteristics are shown considering the presence or absence of constipation and diarrhoea (Table 1). While diarrhoea was found in 44 patients (44.0%) with a median duration of 1 [1–3] day, constipation occurred in 22 patients (22.0%).

While patients with diarrhoea were mainly admitted for respiratory failure (22.7%) with a median APACHE II score of 23 (IQR 10–30), patients without diarrhoea were mostly affected by neurological disorders (25%; $p = 0.002$) with a median APACHE II score of 20 (IQR 4–28; $p = 0.056$). Similarly, patients with constipation were primarily represented by those admitted for trauma (36.4%) with a median APACHE II score of 17 (IQR 5–26), whereas patients without constipation were mainly admitted for respiratory failure (23.1%; $p = 0.036$) with a median APACHE II score of 23 (IQR 4–30; $p = 0.004$).

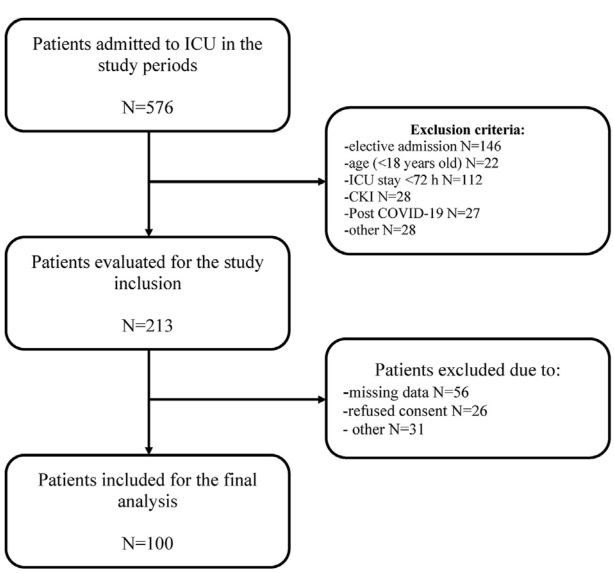

Fig. 1. Study flow chart.
Legend: ICU = intensive care unit, CKI = chronic kidney injury.

Patients without constipation had higher NUTRIC score (6 [0–8] vs. 4 [0–7]; $p < 0.015$), they were more enterally fed (89.7% vs. 77.3%; $p = 0.038$), and received more dietary fiber administration (47.0% vs. 18.2%; $p = 0.003$), as compared with those with constipation. Patients with interruptions of EN were those more frequently allocated to the diarrhoea subgroup (n = 13, 29.5%; $p = 0.033$).

The duration of mechanical ventilation was similar between diarrhoea and non-diarrhoea groups (6 vs 6 days respectively, $p = 0.58$). Similar findings emerged in the constipation group versus the non-constipation group (7 vs 6 days respectively, $p = 0.695$). In addition, only one case of *C. difficile* was diagnosed in the diarrhoea group.

Out of 44 patients with diarrhoea, 21 (47.7%) received diuretics prior to the onset of an episode of diarrhoea, while only 8/56 (14.3%) patients received diuretics but never developed diarrhoea ($p < 0.001$). Diuretics were administered most commonly among the not constipated patients' group (34.6% vs. 9.1%; $p = 0.030$). Moreover, patients receiving insulin therapy during their stay were 33/44 (75.0%) in the diarrhoea group and 22/56 (39.3%) the non-diarrhoea group ($p < 0.001$).

No differences at univariate analysis were found when comparing ICU length of stay, total hospital length of stay, and mortality between diarrhoea and non-diarrhoea or constipation and non-constipation groups, as shown in Table 1.

At multiple logistic regression analysis (Table 2), patients who received diuretics were over 16 times (OR 16.25, IC 1.89–139.86) more likely to develop diarrhoea than patients not receiving diuretics. Trauma patients were more likely to be constipated than patients presenting respiratory failure (OR 23.99, CI 1.38–418.0).

4. Discussion

The main findings of our study are: i) observed diarrhoea incidence aligns with literature; ii) constipation frequency in this patient cohort was lower than that presented in other studies; iii) diuretics use was found to be a strong risk factor for the development of diarrhoea; iv) trauma admission resulted to be a predictor of constipation.

In our cohort of patients, diarrhoea occurred in 44% of the participants, which is a higher percentage when compared to the observational study by Thibault et al. [15]. However, our observed frequency coincides with the majority of the data available in the literature [16]. The wide range of diarrhoea frequency reported in ICUs is mainly due to the different definitions of the term "diarrhoea" employed in research. In fact, there are more than 30 different definitions in the literature [17]. Some of them evaluate frequency of evacuations (>2 or > 3 or >4 stools), while others assess consistency, weight, or duration [18]. A committed effort should be made to identify and implement a common definition of diarrhoea since this could help determining a more precise incidence [12].

On the other hand, constipation was reported in 22% of our patient cohort. Also for this GI disorder, the incidence rate is characterized by a large variability in the literature [19]. Besides incidence and definition, gastrointestinal alterations, with diarrhoea and constipation being the most frequent ones, have important effects on critically ill patients' outcome(s). A recent research based on a systematic review and meta-analysis has reported that diarrhoea was significantly related to ICU adverse outcomes such as mortality (RR 1.43; 95% CI 1.03–1.98), ICU length of stay (mean difference between patients with and without diarrhoea of 8.08 days), and hospital length of stay (mean difference of 9.67 days) [7].

Similar to diarrhoea, available evidence suggests that constipation is associated with prolonged mechanical ventilation,

Table 1
Demographic and baseline characteristics for diarrhoea and non-diarrhoea, constipation and no-constipation groups.

	Overall[a] (N = 100)	Patients with diarrhoea[a] (N = 44)	Patients with no diarrhoea[a] (N = 56)	P-value[b]	Patients with constipation[a] (N = 22)	Patients with no constipation[a] (N = 78)	P-value[b]
General variables							
Age (years)	69.0 [20.0, 89.0]	68.0 [20.0, 89.0]	70.0 [25.0, 89.0]	0.874	69.5 [37.0, 79.0]	68.5 [20.0, 89.0]	0.903
Gender (female)	30 (30.0%)	11 (25.0%)	19 (33.9%)	0.454	7 (31.8%)	23 (29.5%)	1
Admission BMI	26.0 [17.0, 52.0]	27.0 [17.0, 52.0]	26.0 [19.0, 50.0]	0.523	26.0 [20.0, 37.0]	26.0 [17.0, 52.0]	0.834
Reason of admission in ICU							
Respiratory failure	22 (22.0%)	10 (22.7%)	12 (21.4%)	**0.002**	4 (18.2%)	18 (23.1%)	**0.036**
Trauma	16 (16.0%)	4 (9.1%)	12 (21.4%)		8 (36.4%)	8 (10.3%)	
Neurological	19 (19.0%)	5 (11.4%)	14 (25.0%)		5 (22.7%)	14 (17.9%)	
Operative intervention	15 (15.0%)	5 (11.4%)	10 (17.9%)		4 (18.2%)	11 (14.1%)	
Cardiovascular	11 (11.0%)	8 (18.2%)	3 (5.4%)		0 (–)	11 (14.1%)	
Sepsis	9 (9.0%)	4 (9.1%)	5 (8.9%)		1 (4.5%)	8 (10.3%)	
Other	8 (8.0%)	8 (18.2%)	0 (0%)		0 (–)	8 (10.3%)	
APACHE 2 score	21.0 [4.00, 30.0]	23.0 [10.0, 30.0]	20.0 [4.00, 28.0]	0.056	17.0 [5.00, 26.0]	23.0 [4.00, 30.0]	**0.004**
SOFA score	7.00 [1.00, 14.0]	7.00 [2.00, 13.0]	7.00 [1.00, 14.0]	0.272	7.00 [4.00, 12.0]	7.00 [1.00, 14.0]	0.651
Mechanical ventilation	98 (98.0%)	42 (95.5%)	56 (100%)	0.191	22 (100%)	76 (97.4%)	1
MV duration (days)	6 [3–9]	6 [4–11]	6 [3–8]	0.580	7 [3–10]	6 [3–9]	0.695
Clostridium difficile positive	1 (1.0%)	1 (2.3%)	0	0.440	0	1 (1.3%)	1
Nutritional variables							
NUTRIC score	5.00 [0, 8.00]	6.00 [1.00, 7.00]	5.00 [0, 8.00]	0.115	4.00 [0, 7.00]	6.00 [0, 8.00]	**0.015**
EN	87 (87.0%)	39 (88.6%)	48 (85.7%)	0.895	17 (77.3%)	70 (89.7%)	**0.038**
PN	31 (31.0%)	17 (38.6%)	14 (25.0%)	0.212	4 (18.2%)	27 (34.6%)	0.193
Dietary fiber administration	47 (47.0%)	25 (56.8%)	22 (39.3%)	0.123	4 (18.2%)	47 (47.0%)	**0.003**
Patients with interruptions to EN	19 (19.0%)	13 (29.5%)	6 (10.7%)	**0.033**	1 (4.5%)	18 (23.1%)	0.064
Vomiting	18 (18.0%)	9 (20.5%)	9 (16.1%)	0.761	4 (18.2%)	14 (17.9%)	1
GRV >300 mL (at least one event)	42 (42.0%)	19 (43.2%)	23 (41.1%)	1	9 (40.9%)	33 (42.3%)	1
Medications							
Antibiotics	95 (95.0%)	42 (95.5%)	53 (94.6%)	1	20 (90.9%)	75 (96.2%)	0.302
Diuretics	29 (29.0%)	21 (47.7%)	8 (14.3%)	**<0.001**	2 (9.1%)	27 (34.6%)	**0.030**
Enemas	38 (38.0%)	20 (45.5%)	18 (32.1%)	0.248	10 (45.5%)	28 (35.9%)	0.570
Vasopressors	85 (85.0%)	38 (86.4%)	47 (83.9%)	0.955	18 (81.8%)	67 (85.9%)	0.736
Insulin	55 (55.0%)	33 (75.0%)	22 (39.3%)	**<0.001**	8 (36.4%)	47 (60.3%)	0.080
Laxatives	46 (46.0%)	24 (54.5%)	22 (39.3%)	0.187	6 (27.3%)	40 (51.3%)	0.079
NMBs	29 (51.8%)	18 (40.9%)	29 (51.8%)	0.378	11 (50.0%)	36 (46.2%)	0.938
Opioids	97 (97.0%)	43 (97.7%)	54 (96.4%)	1	22 (100%)	75 (96.2%)	1
Non-opioids sedatives	80 (80%)	33 (70%)	47 (83%)	0.267	20 (90%)	60 (77%)	0.147
Prokinetic agents	47 (47.0%)	25 (56.8%)	22 (39.3%)	0.123	7 (31.8%)	40 (51.3%)	0.169
Clinical outcomes							
ICU_{LOS}	7 [5.0, 11.0]	8 [6.0, 12.0]	7 [4.0, 11.0]	0.243	7 [6.0, 14.0]	7 [5.0, 11.0]	0.504
$HOSP_{LOS}$	17 [9.0, 30.0]	17 [12.0, 30.0]	17 [8.0, 31.0]	0.539	15 [7.0, 28.0]	17 [9.0, 31.0]	0.483
Mortality at 180-days	30 (30%)	11 (25%)	19 (34%)	0.333	7 (31.8%)	23 (29%)	0.833

BMI, Body Mass Index; ICU, Intensive Care Unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MV, Mechanical Ventilation; NUTRIC, Nutrition Risk in Critically ill; EN, enteral nutrition; PN, parenteral nutrition; GRV, gastric residual volume; HOSP, Hospital; LOS, Length of Stay.
[a] Data are median [I quartile, III quartile] for continuous variables and number of observations (percentage) for categorical variables.
[b] Differences between the groups were assessed via T-test, Wilcoxon-test, Chi-squared test and Fisher's exact test according to the nature of the variables.

increased infection rates, and ICU length of stay, ultimately leading to worse outcomes [20]. This is not surprising if we consider that Blaser et al. found that overall GI symptoms (including diarrhoea and constipation) in critically ill patients are associated with poor outcomes and independently predict 28-day mortality [21]. This is an important aspect to identify modifiable risk factors in order to avoid GI complications.

The reason for ICU admission was significantly different for patients with and without GI complications.

In our study, cardiovascular instability, for example, was more frequent in patients with diarrhoea than without ($p = 0.002$). On the opposite, trauma was the most frequent reasons for ICU admission in the group of patients with constipation ($p = 0.036$). These results were furtherly confirmed by the multivariable analysis when trauma ICU admission was demonstrated to carry a higher risk for constipation (OR 23.99, CI 1.38–418.0) but a lower risk for diarrhoea (OR 0.07, CI 0–1.28).

These findings could be translated into daily practice implementing active treatments to prevent constipation in patients admitted for trauma in ICUs.

A recent study conducted on 69 severe trauma patients reported that ICU-stay, days of analgesic sedation, muscular relaxation, and mechanical ventilation were risk factors for constipation [22]. We cannot confirm in our study cohort these observations since we did not record more sedatives administration in constipated patients than non-constipated patients, and interestingly similar results were found by Tirlapur et al. [23].

The severity of a critically illness *per se* could be considered a risk factor for GI complications since bowel suffers acute systemic diseases such as other organs, like heart or kidney [24]. In our patient cohort, in fact, the APACHE II score was higher for patients with GI complications ($p = 0.056$ and $p = 0.004$ for diarrhoea and constipation, respectively) that patients without. Nevertheless, these results were not confirmed by a multivariable analysis. As to constipation, results similar to ours were found by Fukuda et al. in a large retrospective observational study where higher APACHE II and SOFA scores were not associated with an increased risk for constipation [10].

Generally, enteral feeding has been considered a risk factor for diarrhoea [25]. However, robust evidences did not confirm this

Table 2
Multivariate logistic regression for predictors of diarrhoea and constipation in critically ill patients.

Predictors	Diarrhoea OR[a] (95% CI)	P-value	Constipation OR[a] (95% CI)	P-value
Reason of admission in ICU: ref = Respiratory failure				
Trauma	0.07 (0–1.28)	0.073	23.99 (1.38–418.03)	**0.029**
Neurological	0.42 (0.05–3.39)	0.413	2.22 (0.14–36.09)	0.574
Operative intervention	0.93 (0.11–8.05)	0.944	0.97 (0.1–9.35)	0.980
Cardiovascular	7.19 (0.62–83.46)	0.115	.	1
Sepsis	0.43 (0.03–5.43)	0.514	1.24 (0.05–31.72)	0.896
Other	.	1	.	1
APACHE 2 score	1.08 (0.92–1.26)	0.376	0.91 (0.76–1.09)	0.313
NUTRIC score	0.98 (0.61–1.6)	0.945	0.83 (0.47–1.47)	0.528
Patients receiving EN (yes vs. no)	0.24 (0.03–2.37)	0.224	0.55 (0.05–5.57)	0.611
EN volume within 48 h	1.0007 (1–1.0014)	0.060	1 (0.99–1.0008)	0.929
Dietary fiber administration (yes vs. no)	0.78 (0.14–4.35)	0.774	0.58 (0.06–5.43)	0.632
Patients with interruptions to EN (yes vs. no)	1.12 (0.11–11.49)	0.926	0.69 (0.02–28.15)	0.843
Diuretics (yes vs. no)	16.25 (1.89–139.86)	**0.011**	0.27 (0.01–8.36)	0.453
Insulin (yes vs. no)	1.87 (0.43–8.06)	0.401	1.51 (0.29–7.93)	0.624
Laxatives (yes vs. no)	3.28 (0.67–16.04)	0.143	0.42 (0.07–2.59)	0.352
Prokinetic agents (yes vs. no)	0.55 (0.11–2.81)	0.475	0.72 (0.12–4.29)	0.718

CI, confidence interval; OR, odds ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; EN, enteral nutrition.
[a] Logistic regression models.

hypothesis, and our results are in line with recent observations [26]. In fact, enteral nutrition in the present study did not increase the risk of diarrhoea or constipation.

Interestingly, enteral formulas containing fibres were associated nor with diarrhoea neither constipation. Whether fibres help reducing GI events [27], especially considering the effect on the colonic mucosa of different types of fibres, i.e. water soluble or not, is still open to debate in literature.

In addition, the modality of EN administering plays a role. In our study, only continuous infusion was used. This method is the preferred way because it is easy to manage and reduces nurses' workload. However, some side effects are detected: lower energy provided, restriction of patients' mobility, risk of feeding intolerance, and lower anabolic capacity [28]. For this reason, a recent study investigated whether intermittent enteral feeding could be a valid alternative over continuous infusion [29]. No valid conclusions, however, could be achieved so far.

Prokinetic agents and laxatives are frequently used in ICU to manage gastrointestinal disorders [30]. When prokinetic drugs are used during intragastric feeding in ICU, metoclopramide was associated with diarrhea in 32%, erythromycin in 30%, and their combination in 49% of the study population, as indicated by Nguyen et al. [31].

We did not find the same relationship between prokinetics and laxatives; in fact, in our study, they did not increase the risk of bowel movement disorders. However, this should be considered with caution since we did not perform a randomized trial, so some biases could have been missed.

An interesting finding is that diuretics were strongly associated with diarrhea (OR 16.25, CI 1.89–139.86). This result needs to be investigated more in detail since diuretics are very frequently used in ICUs [32]. We argue that diuretics (in our study represented for by >90% by furosemide) can cause extracellular fluid volume contraction, hypovolemia, and consequently electrolyte loss with altered gut function [33]. Moreover, we cannot exclude that electrolytes disturbances caused by diuretics may favor gut dysmotility [34]. This should prompt attention in physicians about the use of diuretics, and a proper prescription should be contemplated, especially if diarrhea is already present.

Our study presents some limitations. First, this study evaluated GI complications in a single centre, therefore the results may not be completely generalized. In fact, nutritional and bowel management habits can differ due to dissimilar hospital protocols or specialties. Second, the entire composition of enteral formulas was not considered in the analysis. However, all formulas used had low osmolarity (<370 mOsm/L), limiting possible GI alterations [35]. Third, due to the observational design of this study, clinical outcomes such as ICU-mortality, ICU-length of stay, and hospital mortality should be considered with caution since they were not properly evaluated. Finally, microbiota compositions were not investigated, and therefore some causes of GI alterations could have been missed.

5. Conclusion

In our cohort the incidence of diarrhoea in critically ill patients was 44.0%, while constipation 22.0%. The main predictor of constipation was trauma admission and the main predictor of diarrhoea was the use of diuretics. This study underlines that GI complications in ICU are a widespread phenomenon that should be considered in the management of critically ill ICU patients. Further larger randomized controlled trials are needed to confirm our results and to clarify the complex phenomena associated with GI complications in ICU.

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Declaration of competing interest

All Authors have nothing to declare.

CRediT authorship contribution statement

Matteo Danielis: Conceptualization, Data curation, Investigation, Methodology, Writing-original draft. **Elisa Mattiussi**: Conceptualization, Data curation, Investigation, Methodology, Writing-review & editing. **Tommaso Piani**: Investigation, Methodology, Writing-review & editing. **Anna Iacobucci**: Investigation, Methodology, Writing-review & editing. **Annarita Tullio**: Data analysis and curation. **Alessio Molfino:** Data curation, Methodology, Writing-review & editing. **Luigi Vetrugno**: Methodology, Writing-review & editing. **Cristian Deana**: Conceptualization, Data curation, Investigation, Methodology, Writing-original draft. **Luigi Vetrugno** and **Cristian Deana** share last authorship.

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