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The incidence and risk factors of gastrointestinal dysfunction during enteral nutrition in mechanically ventilated critically ill patients

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Abstract

Aim: To assess the occurrence and risk factors of gastrointestinal (GI) dysfunction during enteral nutrition (EN) in critically ill patients supported with mechanical ventilation.

Design: Prospective observational study.

Methods: Totally 252 patients admitted at a mixed medical-surgical ICU were enrolled. GI symptoms and the potential risk variables were recorded during the first 14 days of EN.

Results: The incidence of GI dysfunction was 65.5%, and the incidence of diarrhoea, constipation, abdominal distension, and upper GI intolerance was 28.2%, 18.3%, 6.7% and 12.3%, respectively. The median onset days of constipation, diarrhoea, abdominal distension and UDI was 3, 5, 5 and 6 days, respectively. Multivariable Cox regression analysis showed a significant relationship between GI dysfunction and age (HR = 2.321, 95% CI: 1.024–5.264, $p = 0.004$), APACHE-II score at ICU admission (HR = 7.523, 95% CI: 4.734–12.592, $p = 0.018$), serum albumin level (HR = 0.594, 95% CI: 0.218–0.889, $p = 0.041$), multidrug-resistant bacteria-positive culture (HR = 6.924, 95% CI: 4.612–10.276, $p < 0.001$), negative fluid balance (HR = 0.725, 95% CI: 0.473–0.926, $p = 0.037$), use of vasopressor drugs (HR = 1.642, 95% CI: 1.297–3.178, $p < 0.001$), EN way (HR = 6.312, 95% CI: 5.143–11.836, $p < 0.001$), infusion rate (HR = 1.947, 95% CI: 1.135–3.339, $p < 0.001$), and intra-abdominal hypertension (HR = 3.864, 95% CI: 2.360–5.839, $p < 0.001$).

Conclusion: Critically ill patients supported with mechanical ventilation are at a high risk of GI dysfunction. Interventions such as the use of laxatives or prokinetic agents, control of EN infusion rate, and maintaining a normal state of hydration, might be beneficial for the prevention of GI dysfunction in critically ill patients.

Patient or Public Contribution: No.

KEYWORDS
enteral nutrition, gastrointestinal dysfunction, intensive care unit, intra-abdominal pressure, mechanical ventilated

1 | INTRODUCTION

Patients in intensive care units (ICU) are usually admitted for respiratory failure, renal insufficiency, severe trauma, shock, severe infection, and so on (Mohr et al., 2020). More than 80% of these patients require a ventilator to maintain normal ventilation (Ramachandran et al., 2020). These patients are usually in a state of hyper-catabolism and reduced anabolism, with increased energy and protein consumption (Tian et al., 2017; van Zanten et al., 2019). The situation increases the systemic inflammatory response and infection-related morbidity, multiple organ dysfunction, hospital stays and mortality (Hiura et al., 2020; Magnette et al., 2015; Weijs et al., 2014). It is reported that malnutrition is occurred in about 38%–78% of ICU patients (Lew et al., 2017). Malnutrition diagnosed by nutrition assessments is associated with longer length of ICU stay, increased cost of hospitalization, more frequent ICU readmission, higher incidence of infection, and higher risk of hospital mortality (Efremov et al., 2021; Hiura et al., 2020; Ross et al., 2017). Therefore, nutritional support therapy is very essential for critically ill patients.

Enteral nutrition (EN) is recommended as the first choice of nutritional support therapy, which is beneficial to maintain the normal structure and physiological function of GI mucosa (Allen & Hoffman, 2019; Jordan & Moore, 2020). In addition, the application of EN could improve GI peristalsis to ensure adequate blood supply, thus maintaining gut integrity and immunity (Ding et al., 2015; Hegazi & DeWitt, 2014). Existing guidelines recommended initiating EN within 24–48 h after ICU admission if patients cannot eat (Reintam Blaser et al., 2017; Taylor et al., 2016). Studies have demonstrated that early EN has several advantages, including protecting intestinal mucosal integrity, reducing infection rates, and attenuating morbidity (Shankar et al., 2015; Yu et al., 2021).

However, plans to provide adequate and timely nutritional supplies to critically ill patients are often hindered by gastrointestinal (GI) motility disorders and complications associated with EN. The incidence of GI dysfunction during EN has been reported as high as 30.5%–63.0% in critically ill patients, and even higher in mechanically ventilated patients, ranging from 50.0% to 88.9% in Atasever et al. (2018), Hill (2019), Lin et al. (2018), McClave et al. (2020) and Reintam Blaser et al. (2012). Previous studies (Efremov et al., 2021; Heyland et al., 2021; Hopkins et al., 2020) have proved that enteral feeding intolerance has a significant negative impact on patients' nutritional status and clinical outcomes, especially when it occurs for multiple days. Medical staff has taken many interventions to reduce the incidence of GI dysfunction, including raising the bed tilt angle, changing the feeding patterns, heating the nutrition, using a specialized enteral formula. However, GI dysfunction events are still very common (Hopkins et al., 2020; Qiu et al., 2017). GI dysfunction causes critically ill patients to fail to reach the feeding attempt at the set time and increases the risk of malnutrition (Tatsumi, 2019). Evidence suggests that these patients are at increased risk of readmission if discharged with ongoing GI dysfunction (Whitlock et al., 2010).

Till now, there is no widely used objective methodology to measure GI dysfunction. Because of the difficulty of clinically assessing immune function and the efficacy of digestion and absorption, the GI dysfunction assessment in patients focuses mainly on the GI clinical symptoms, such as constipation, delayed gastric emptying, diarrhoea, and vomiting (Hill, 2019). Until now, the factors affecting GI function during EN implementation have not been fully explored. Thus, this prospective observational study aimed to evaluate the incidence and risk factors of GI dysfunction in patients receiving EN within the first 14 days in ICU. It was hoped that the findings of this study could help develop precautions to prevent GI dysfunction.

2 | METHODS

2.1 | Study design, sample and setting

This was a prospective observational study. Patients were recruited by convenience sampling at a mixed medical-surgical ICU of Huizhou Central People's Hospital between June 2019 and May 2021. According to the following criteria, patients were enrolled in this study: aged 14 or above, supported with mechanical ventilation and EN within 48 h of ICU admission, ICU stay >48 h. Patients with GI bleeding, enterostomy or colostomy, GI symptoms within 48 h of ICU admission, and using laxatives were excluded. Patients were also excluded if they no longer need mechanical ventilation support during the observational period.

Sample size was estimated using the PASS version 2021 software. According to the study objective and study design, Procedure "Confidence intervals of one proportion" was selected for sampling calculation. Based on a previous study (Atasever et al., 2018), a sample proportion of 63%, a confidence interval width of 0.15 and an alpha of 0.05 were set. This suggested that 195 participants were required. Patients in ICU have a rapid change of disease condition, which may lead to more dropout. Therefore, 260 patients were required in this study considering a 25% dropout rate.

2.2 | Measurement and data collection

According to The Working Group on Abdominal Problems (WGAP) of the European Society of Intensive Care Medicine (ESICM), GI dysfunction refers to vomiting, diarrhoea, GI bleeding, diminished or absent bowel sounds, constipation, higher gastric residuals (gastric residual volume ≥500 mL/24 h) (Reintam Blaser et al., 2012). In this study, no patients developed GI bleeding 48 h after admission to ICU. The observed GI dysfunction in this study included abdominal distention, diarrhoea, constipation, or upper digestive intolerance (UDI). *Abdominal distension* was defined as increased abdominal girth, abdominal muscle tension, drum sound on percussion, and increased intra-abdominal pressure (IAP) (greater than or equal to 12 mmHg for two consecutive measurements within 6 h). *Diarrhoea* was defined as the elimination of at least three liquid stools per

day. *Constipation* was defined as a frequency of faeces evacuation of fewer than three times in a week, no faeces evacuation for more than 3 days, hard stool or difficult passage of stool, or need for laxatives. *UDI* was recognized when the gastric aspirate volume (GAV) was more than 500 mL/24 h, or when the GAV was more than 150 mL on two consecutive measurements, or when two or more times vomiting occurred. The patient's observation and recording were terminated if the patient was determined to have GI dysfunction or the observation period exceeded 14 days.

The potential predisposing risk factors of GI dysfunction were also documented: patients' characteristics, disease-related factors, treatment-related factors, and enteral-nutrient-related factors. (1) patients' characteristics, including age, gender and body mass index (BMI), were recorded within 48 h after ICU admission. (2) Disease-related factors included principal disease diagnosis, acute physiology and chronic health evaluation II (APACHE-II) score, blood glucose (measured and recorded every 6 h), serum albumin level within 48 h prior to EN initiation, and intra-abdominal pressure. Hyperglycemia was defined as two consecutive random blood glucose level above 11.1 mmol/L. IAP is defined as the steady-state pressure concealed within the abdominal cavity resulting from the interaction between the viscera and abdominal wall (Milanesi & Caregnato, 2016). It was measured by trans-bladder measurement at end-expiration in the supine position after ensuring that abdominal muscle contractions were absent and with the transducer zeroed at the level of the mid-axillary line (Kirkpatrick et al., 2013). Intra-abdominal hypertension (IAH) was defined as IAP greater than or equal to 12 mmHg for two consecutive measurements within 6 h. (3) Treatment-related factors including multidrug-resistant (MDR) bacteria-positive culture, the use of antibiotics, sedatives and vasopressor drugs were recorded according to the presence. Mechanical ventilation mode and positive end-expiratory pressure (PEEP) were recorded when it was changed. The fluid balance (Thongprayoon et al., 2016) state was calculated from ICU admission to the end of the prospective observation. (4) EN parameters including infusion rate and EN way (gastric EN or post-pyloric EN) were also recorded as potential risk factors for GI dysfunction. The infusion rate was the total amount of enteral nutrients injected divided by the total infusion time. Infusion rate on the day of onset of GI dysfunction or on the last day of observation period in patients without GI dysfunction was used for analysis.

2.3 | Feeding protocol

The energy target was set at 25 kcal/kg/day according to the American Society for Parenteral and Enteral Nutrition guideline. Patients were fed by EN as soon as possible if they had a functional GI tract and were unable to eat orally. EN was administered continuously at a constant rate by using a feeding pump. The initial feeding rate was 20 mL/h, and then increased gradually to an appropriate rate for each patient. The temperature of EN product was controlled at 37–42 centigrade. GAV was measured by aspirating with a 50 mL syringe before starting EN and every 6 h from Day 1 to the end of the study observation. Aspirate was returned to the patient unless it exceeded 250 mL.

2.4 | Data analysis

All data analysis was performed using SPSS 23.0 software. Quantitative data were presented as mean ± standard deviation or quartiles [M(P_{25}, P_{75})] according to their distribution, and categorical data were presented as frequency and percentage. Intergroup comparison of quantitative data was conducted by independent sample Student's *t*-test or non-parametric test, while intergroup comparison of categorical data was conducted by the chi-square test. Variables in univariable analysis with a $p < 0.05$ and some clinically important variables were included for Cox regression analysis. Variables included in the Cox regression equation with a $p < 0.05$ were considered to be risk factors of GI dysfunction.

2.5 | Ethical considerations

The study was approved by the Medical Ethics Committee, and all procedures involving human participants were in accordance with the ethical standards of the national research committee and the 1964 Helsinki Declaration. Written informed consent was obtained from the patients or their legal guardians.

3 | RESULTS

3.1 | Characteristics of patients

A total of 271 patients who met the inclusion and exclusion criteria were initially enrolled in this study, but 19 patients were excluded because they no longer needed mechanical ventilation ($n = 11$) or died during the observational period ($n = 8$). Finally, 252 were included in the analysis. Of these, 155 (61.5%) were male and 97 (38.5%) were female, with a mean age of 62.6 ± 13.4 years. Among the included patients, the principal diagnosis was respiratory disease in 94 patients, cardiac diseases in 64 patients, neurological disease in 41 patients, kidney failure in 34 patients and other diseases in 19 patients. The principal diagnosis categories were listed in Table 1.

3.2 | Incidence of GI dysfunction

In total, 165 patients were identified with GI dysfunction, with an incidence of 65.5%. Patients diagnosed with respiratory disease had a higher incidence of GI dysfunction (73.4%), and patients diagnosed with cardiac disease had a lower incidence of GI dysfunction (54.7%). Diarrhoea occurred in 71 (28.2%) patients, constipation occurred in 46 (18.3%) patients, abdominal distension occurred in 17 (6.7%) patients, and UDI occurred in 31 (12.3%) patients. More

TABLE 1 Principal diagnosis categories for patients with and without GI dysfunction.

Diagnosis	Group 1	Group 2	GI dysfunction incidence (%)
Respiratory	25	69	73.4
Cardiac	29	35	54.7
Neurological	14	27	65.9
Renal failure	13	21	61.8
Others	6	13	68.4
Total	87	165	65.5

Abbreviations: GI, gastrointestinal; Group 1, without GI dysfunction; Group 2, with GI dysfunction.

TABLE 2 Incidence of GI dysfunction during the first 14 days of the ICU stay.

Symptoms of GI dysfunction	Number of patients	Incidence (%)
Diarrhoea	71	28.2
Constipation	46	18.3
Abdominal distension	17	6.7
UDI	31	12.3
GAV>500 mL/24 h or GAV>250 mL/6 h	22	8.7
Vomiting	9	3.6

Abbreviations: GAV, gastric aspirate volume; GI, gastrointestinal; UDI, upper digestive intolerance.

information was listed in Table 2. The median onset days of constipation, diarrhoea, abdominal distension and UDI was 3, 5, 5 and 6 days, respectively.

3.3 | Univariate analysis of risk factors for GI dysfunction

Independent sample *t*-test, non-parametric test and Chi-square test were used to compare the characteristics between patients with and without GI dysfunction. The results showed that patients with GI dysfunction were older ($t=-4.555$, $p<0.001$), had higher BMI score ($t=-5.411$, $p<0.011$) and APACHE-II score ($z=-2.342$, $p=0.019$) at admission than those without GI dysfunction. There was no statistical significance in GI dysfunction incidence among patients of different gender ($\chi^2=0.019$, $p=0.893$), time from ICU admission to EN initiation ($z=-1.268$, $p=0.071$). Patients with hyperglycemia or diabetes ($\chi^2=7.408$, $p=0.006$), in MDR bacteria-positive culture ($\chi^2=3.923$, $p=0.048$), or positive fluid balance state ($\chi^2=7.114$, $p=0.008$) were more likely to develop GI dysfunction. Patients with low serum albumin levels were more likely to develop GI dysfunction ($t=6.880$, $p<0.001$). The use of vasopressor drugs was also associated with the development of GI dysfunction ($\chi^2=14.427$, $p<0.001$). Using gastric EN ($\chi^2=52.106$, $p<0.001$), higher EN infusion rate ($z=-3.042$, $p<0.001$) and IAH ($\chi^2=7.654$, $p=0.006$) were also related with GI dysfunction. Mechanical ventilation mode ($\chi^2=0.367$, $p=0.832$) was not associated with GI dysfunction, but the higher PEEP parameter ($t=-2.261$, $p=0.025$) was associated with GI dysfunction. See Table 3 for more details.

3.4 | Multivariable Cox regression analysis for GI dysfunction

The multivariable Cox regression model showed significant a significant relationship between GI dysfunction and age (HR=2.321, 95% CI: 1.024–5.264, $p=0.004$), APACHE-II score at ICU admission (HR=7.523, 95% CI: 4.734–12.592, $p=0.018$), serum albumin level (HR=0.594, 95% CI: 0.218–0.889, $p=0.041$), MDR bacteria-positive culture (HR=6.924, 95% CI: 4.612–10.276, $p<0.001$), negative fluid balance (HR=0.725, 95% CI: 0.473–0.926, $p=0.037$), use of vasopressor drugs (HR=1.642, 95% CI: 1.297–3.178, $p<0.001$), EN way (HR=6.312, 95% CI: 5.143–11.836, $p<0.001$), infusion rate (HR=1.947, 95% CI: 1.135–3.339, $p<0.001$), and IAH (HR=3.864, 95% CI: 2.360–5.839, $p<0.001$). See Table 4 for more information.

4 | DISCUSSION

4.1 | The incidence of GI dysfunction

In this study, the incidence of GI dysfunction in ICU patients supported with mechanical ventilation was 65.5%. GI function was mainly associated with age, APACHE-II, serum albumin level, MDR bacteria culture, fluid balance, vasopressor drugs use, IAP, EN way and infusion rate. This study conducted a comprehensive analysis of risk factors for GI dysfunction, which could provide essential data for clinical interventions development. We also found that patients with a principle diagnosis of respiratory disease were more likely to develop GI dysfunction. And the incidence of diarrhoea was the highest (28.2%). The occurrence of diarrhoea would damage the perianal skin and increase the risk of decubitus ulcers, delaying patient recovery (Labeau et al., 2021). In addition, diarrhoea has increased nurses' workload and the economic burden of hospitals (Williams et al., 2014). Therefore, taking precautionary measures for incipient episodes of diarrhoea and targeted treatment for existing diarrhoea was essential for reducing the burden on patients and hospitals.

4.2 | The associated factors of GI dysfunction

In this study, the average age of patients with GI dysfunction was 65.3 ± 11.9 years, much higher than the mean age (57.4 ± 15.1 years) of patients without GI dysfunction. The result was consistent with previous studies (Heyland et al., 2021; Shan et al., 2018). With the

TABLE 3 Univariate analysis of risk factors for GI dysfunction among ICU patients.

Variables	Group 1	Group 2	$t/\chi^2/z$	*p*
Age [year, $\bar{x} \pm s$]	57.4 ± 15.1	65.3 ± 11.9	−4.555	<0.001
Male [*n* (%)]	53 (60.9)	102 (61.8)	0.019	0.893
BMI [kg/m^2, $\bar{x} \pm s$]	22.8 ± 3.7	25.5 ± 3.8	−5.411	<0.001
APACHE-II score at ICU admission, M(P_{25}, P_{75})]	20 (11, 42)	29 (12, 51)	−2.342	0.019
Time from ICU admission to EN initiation [h, M(P_{25}, P_{75})]	12 (5, 18)	14 (7, 23)	−1.268	0.071
Hyperglycemia or diabetes [*n* (%)]	19 (21.8)	64 (38.8)	7.408	0.006
Serum albumin within 48 h prior to EN initiation [g/L, $\bar{x} \pm s$]	37.2 ± 5.0	32.4 ± 5.4	6.880	<0.001
MDR bacteria-positive [*n* (%)]	11 (12.6)	38 (23.0)	3.923	0.048
Negative fluid balance [*n* (%)]	58 (66.7)	81 (49.1)	7.114	0.008
Use of antibiotics [*n* (%)]	74 (85.1)	151 (91.5)	2.483	0.088
Use of sedatives [*n* (%)]	64 (73.6)	134 (81.2)	0.457	0.312
Use of vasopressor drugs [*n* (%)]	48 (55.2)	129 (78.2)	14.427	<0.001
EN way			52.106	<0.001
Gastric EN [*n* (%)]	47 (54.0)	153 (92.7)		
Post-pyloric EN [*n* (%)]	40 (46.0)	12 (7.3)		
EN infusion rate [mL/h, M(P_{25}, P_{75})]	50 (35, 65)	55 (45, 70)	−3.042	0.005
IAH [*n* (%)]	31 (35.6)	89 (53.9)	7.654	0.006
Ventilation mode			0.367	0.832
PSV [*n* (%)]	18 (20.7)	35 (21.2)		
A/C [*n* (%)]	46 (52.9)	92 (55.8)		
SIMV [*n* (%)]	23 (26.4)	38 (23.0)		
PEEP [cmH_2O, $\bar{x} \pm s$]	4.7 ± 1.4	5.1 ± 1.3	−2.261	0.025

Abbreviations: A/C, assist/control; APACHE-II, acute physiology and chronic health evaluation II; BMI, body mass index; EN, enteral nutrition; GI, gastrointestinal; Group 1, without GI dysfunction; Group 2, with GI dysfunction; IAH, intra-abdominal hypertension; MDR, multidrug resistant; PSV, pressure support ventilation; SIMV, synchronized intermittent mandatory ventilation.

growth of age, the function of body is gradually degraded, and the GI mucosa is atrophied to varying degrees (Vanheel & Farré, 2013). GI peristalsis is weakened and the empties are delayed, which affects the absorption and transport of water and electrolyte (Vanheel & Farré, 2013). In addition, there are some differences in the gut microbial composition among patients of different ages (Lee et al., 2021). This might be why older patients are more prone to develop GI dysfunction.

APACHE-II score has been widely used in ICU to assess the disease severity and predict the prognosis of critically ill patients. This study revealed that patients with higher APACHE-II score at ICU admission were at higher risk for GI dysfunction during EN. Severe disease severity usually results in a high-stress response and causes more severe stress GI injury (Reintam Blaser et al., 2012). Stress response would delay gastric empties, impair gastroduodenal motility, alter gastric secretions and pancreatic fluid output, intestinal transport and colonic motility (Bhattacharyya et al., 2014; Reintam Blaser et al., 2012). In addition, when patients are critically ill, the GI blood flow would decrease obviously, and the subsequent injury caused by ischemia and hypoxia would lead to GI dysfunction (Huang et al., 2012).

Consistent with the results reported in previous studies (Atasever et al., 2018; McClave et al., 2020; Shan et al., 2018), the present study also found that low serum albumin levels were associated with higher risk of GI dysfunction. Most patients with mechanical ventilation were in a state of stress, and the protein and energy stores could be rapidly broken down (Allen & Hoffman, 2019). Then the decrease of serum albumin would lead to increased catabolism in patients, which might aggravate GI mucosal oedema and cause secondary lymphatic dilatation (van der Velden et al., 2013). Intestinal leakage would lead to oedema of the intestinal wall and a slowing of peristalsis, which might cause GI symptoms such as nausea, vomiting and diarrhoea (Levitt & Levitt, 2017). The administration of intravenous fluids is widely regarded as the first step in the resuscitation of the critically ill but would dilute serum albumin levels (Malbrain et al., 2014). However, the serum albumin level of critical illness patients is in a fluctuating state. To further explore the relationship between the

TABLE 4 Multivariable Cox regression analysis for GI dysfunction in patient supported with mechanical ventilation.

Variable	*B*	SE	Wald	*p*	HR (95% CI)
Age	0.842	0.418	4.064	0.004	2.321 (1.024, 5.264)
APACHE-II score at ICU admission	2.312	1.362	3.945	0.018	7.523 (4.734, 12.592)
Serum albumin within 48 h prior to EN initiation	−0.846	0.760	1.396	0.041	0.594 (0.218, 0.889)
Negative fluid balance (reference: no)	−0.594	0.670	1.664	0.037	0.725 (0.473, 0.926)
IAH (reference: no)	1.399	0.365	14.253	<0.001	3.864 (2.360, 5.839)
MDR bacteria-positive (reference: no)	1.934	0.572	10.142	<0.001	6.924 (4.612, 10.276)
Use of vasopressor drugs (reference: no)	0.472	0.210	12.651	<0.001	1.642 (1.297, 3.178)
EN way (reference: post-pyloric EN)	1.762	0.594	9.737	<0.001	6.312 (5.143, 11.836)
EN infusion rate	0.851	0.231	12.469	<0.001	1.947 (1.135, 3.339)

Abbreviations: APACHE-II, acute physiology and chronic health evaluation II; CI, confidence interval; EN, enteral nutrition; GI, gastrointestinal; HR, hazard ratio; IAH, intra-abdominal hypertension; MDR, multidrug resistant; SE, standard error.

alteration of serum albumin level and the risk of GI dysfunction might be necessary.

Critically ill patients are often treated with antibiotics, sedatives, and vasopressor drugs, which have been known to impair GI motility (Stupak et al., 2012). In this study, the incidence of GI dysfunction was increased in patients receiving vasopressor drugs, which was consistent with previous studies (Atasever et al., 2018; Nguyen, 2014). Adequate fluid rehydration is the first intervention for critically ill patients with hypotension, tissue hypoperfusion, and microcirculation disorders. If the blood pressure is still below the target value, vasopressor drugs may be considered to raise the blood pressure. However, the use of vasopressor drugs would further aggregate the situation of GI ischemia, leading to severe GI dysfunction. Inconsistent with the result of other studies (Atasever et al., 2018; Mentec et al., 2001), there was no association between antibiotic use and GI dysfunction in the multivariable analysis in this study. However, we found that patients with MDR bacteria-positive culture were more likely to develop GI dysfunction. The discrepancy could be due to antibiotic usage and change in the microbiome. It has been reported that the prevalence of MDR bacteria-positive in ICU is as high as 31.2% (Gill et al., 2016). The problem of MDR bacteria-positive has always been a clinical concern, but there have been few developments in the last decades in antimicrobials (Lee et al., 2017). Before the development of novel, target bacterial therapies, it is vital and recommended to avoid the unnecessary use of strong empiric antibiotics.

Intravenous fluid is an important therapy for the resuscitation of critically ill patients, but large volume intravenous fluid may be harmful to unstable patients. Multiple studies (Malbrain et al., 2014; Thongprayoon et al., 2016) have approved that a positive fluid balance is associated with impaired organ function and may increase the risk of death. Positive fluid balance results in tissue oedema, which impairs oxygen and metabolite diffusion, distorts tissue architecture, impedes capillary blood flow and lymphatic drainage, and disturbs cell–cell interactions (Marik, 2014). Moreover, positive fluid balance results in capillary leak, which contributes to the genesis of IAH, reduces bowel contractility and peristalsis and increases complications such as intestinal oedema, malabsorption and increased intestinal permeability (Malbrain et al., 2014). This is a pathophysiological explanation of the effect of positive humoral balance on the GI tract. Studies have proved that negative fluid balance helps reduce the burden on organs and predict survival (Malbrain et al., 2014; Murphy et al., 2009). Therefore, clinicians must maintain a heightened awareness of the dynamic relationship between fluid balance, IAH and abdominal symptoms. Measurement of IAP could provide an additional numeric value to detect dynamics of IAP during EN in patients with hypoperfusion or fluid overload.

In this study, we found that post-pyloric EN was a more effective mean to reduce GI dysfunction incidence compared with gastric EN. Gastric access is recommended as the standard approach to initiate EN, and post-pyloric EN is recommended for patients with gastric feeding intolerance not solved with prokinetic agents and with a high risk for aspiration (Taylor et al., 2016). A study has proved that patients would benefit from post-pyloric EN, such as reducing the risk of ventilator-acquired pneumonia and aspiration (Dhaliwal et al., 2014). However, post-pyloric tube placement requires more expertise, and it is considered less physiologic than gastric EN. Therefore, we suggest gastric access as the standard, and implementing post-pyloric access only in patients with a high risk of aspiration, large (>500 mL) GRV and intolerance to gastric feeding. We also found that the infusion rate of

EN was associated with the occurrence of GI dysfunction. The guideline (Reintam Blaser et al., 2017) recommends that EN should start at a low initial rate (10–20 mL/h) and increase slowly while carefully monitoring GI symptoms. Most feeding protocols are based on providing EN for continuous 24 h with a set rate but are frequently stopped for various reasons, causing a lower amount of energy delivery than what is prescribed. This is also an important factor to be considered during implementing EN. For the patients with GI dysfunction, EN should be either continued at a slow rate or ceased depending on the severity of clinical symptoms (Reintam Blaser et al., 2017). Meanwhile, intravenous nutrition should be considered to ensure nutritional supplementation for patients.

4.3 | Limitations of the study

This study also had some limitations. Until now, there is no clear, widely agreed-upon definition available for GI dysfunction. In this study, we set a relatively specific definition of GI symptoms. But it needed further recognition from other scholars. In further research, a detailed and widely agreed-upon definition was required to improve knowledge and develop interventions for GI dysfunction. Besides, the incidence and related factors of GI dysfunction varied among patients with different diseases diagnoses, and the associated factors of different GI symptoms might be different. Due to the limited sample size, we did not conduct a stratified analysis. Thirdly, this study was single-centre study, the validity of the findings needed further verification. Multi-centre studies should be carried out in the future to avoid the selection bias existing in single-centre studies.

5 | CONCLUSION

The study findings highlight the high prevalence of GI dysfunction in mechanically ventilated patients during EN. GI dysfunction is associated with elder age, higher APACHE-II score, lower serum albumin level, MDR bacteria-positive culture, and higher intra-abdominal pressure. Interventions such as the use of laxatives or prokinetic agents, control of EN infusion rate, and maintaining a normal state of hydration, might be beneficial for the prevention of GI dysfunction for critically ill patients. In future, there is a need for more prospective studies to compare different management strategies and intervention for GI dysfunction in critically ill patients.

AUTHOR CONTRIBUTIONS

Study design: Ling Shi, Jianmei Shao, Yuxia Luo. *Data collection*: Ling Shi, Jianmei Shao, Guiyan Liu, Miao OuYang. *Data analysis*: Ling Shi, Jianmei Shao. *Manuscript writing*: Ling Shi, Jianmei Shao.

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CONFLICT OF INTEREST STATEMENT

Ling Shi, Jianmei Shao, Yuxia Luo, Guiyan Liu and Miao OuYang declare that no conflict of interest exists in the submission of this manuscript, and the manuscript is approved by all authors for publication, and the article has not been published previously, not under consideration for publication elsewhere, in whole or in part.

DATA AVAILABILITY STATEMENT

Data available on request from the corresponding author (Email: 377481925@qq.com).

ETHICS STATEMENT

All procedures performed in the study involving human participants were in accordance with the ethical standards of the hospital, the national research committee, and the 1964 Helsinki declaration (as revised in Brazil 2013). The study was approved by the Medical Ethics Committee of Huizhou Central People's Hospital, and informed consent was received from each participant or their statutory guardian.

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