Original Article

Prevalence and Risk Factors of Enteral Feeding Intolerance in Critically Ill Patients and the Effectiveness of Preventive Treatments: A Prospective Study

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Abstract

Background: Feeding intolerance (FI) is a prevalent cause of enteral nutrition (EN) disruption. Factors that can prevent FI are poorly described.

Objectives: To determine the prevalence and risk factors associated with FI in critically ill patients and the effectiveness of preventive treatments.

Patients and Methods: This prospective observational study included critically ill patients admitted to the ICU of a general hospital who received EN through a nasogastric or nasointestinal tube from March 2020 to October 2021. Independent sample *t*-test, repeated measurement analysis of variance, and multivariate analysis were used to explore independent risk factors and the efficacy of preventive treatments.

Results: The study included 200 critically ill patients (mean age: 59.1 ± 17.8 years), of whom 131 were male. Most patients (58.50%) developed FI after a median EN duration of 2 days. The independent risk factors for FI were fasting for >3 days, high APACHE II score, and acute gastrointestinal injury (AGI) grade I before EN ($P < 0.05$). During EN, whole protein was found to be an independent preventive treatment that significantly decreased FI ($P < 0.05$), while before EN, early use of enema and gastric motility drugs in patients with abdominal distention/constipation significantly decreased FI (for both, $P < 0.05$). The preventive treatment group had significantly higher intake of the nutrient solution and significantly shorter invasive mechanical ventilation duration than the without preventive treatment group (for both, $P < 0.05$).

Conclusion: In ICU patients receiving nasogastric or nasointestinal tube feeding, FI was frequent, occurred early, and was more frequent in patients with fasting >3 days, a high APACHE II score, and an AGI grade before EN. Preventive treatments can reduce FI prevalence and result in patients consuming more nutrient solutions and having shorter invasive mechanical ventilation duration.

Chinese Clinical Trial Registry Registration no: ChiCTR-DOD-16008532.

Keywords: APACHE II, critical care, effect factors, enteral feeding intolerance, enteral nutrition, preventive treatments

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INTRODUCTION

Feeding intolerance (FI) is a common cause of enteral nutrition (EN) disruption. According to the definitions of Working Group on Abdominal Problems (WGAP) of the European Society of Intensive Care Medicine (ESICM), FI is a general term describing an intolerance to enteral feeding (resulting in complications such as vomiting, high gastric residuals, diarrhea, gastrointestinal bleeding, or enterocutaneous fistulas) due to any clinical reason. FI should also be considered present if at least 20 kcal/kg bodyweight/day via the enteral route cannot be reached within 72 hours.[1]

In 2021, the Chinese Critical Care Nutrition Trials Group developed a novel FI score that included three categories: abdominal distention/pain, nausea/vomiting, and diarrhea. Each category was divided into four grades, with stepped-up scores (0, 1, 2, and 5 points) reflecting the severity of potential FI.[2] In addition, the gastrointestinal dysfunction score was developed for critically ill patients and contained the following five parts: no risk, increased risk, gastrointestinal dysfunction, gastrointestinal failure, and life-threatening. The gastrointestinal dysfunction score was developed based on the rationale of the previously developed acute gastrointestinal injury (AGI) grading system, which is also helpful in assessing FI.[3]

FI has been reported to occur in about one-third of the cases after EN initiation, and this increases with the length of intensive care unit (ICU) stay and is linked to mortality.[4,5] In terms of the risk factors associated with FI, Nguyen NQ *et al.*[6] found that patients with blood glucose levels >10 mmol/L could have aggravated gastroparesis symptoms and delayed gastric emptying, causing FI. In addition, mechanical ventilation, especially in patients with positive end-expiratory pressure, can cause gastrointestinal tract ischemia and induce FI.[7-9] Moreover, FI treatment or prevention is more important for the nutritional outcomes of critically ill patients. However, preventive treatments for FI are poorly described. Furthermore, the effect of preventive treatments lacks in-depth analysis for critically ill patients with multiple FI risk factors.

This study aimed to estimate the prevalence of FI in critically ill patients receiving EN as well as to evaluate the risk factors, identify the main preventive treatments and their effects, and characterize the independent risk factors of FI in these patients.

MATERIALS AND METHODS

Study design, setting, and participants

This prospective study included critically ill patients who were admitted to the ICU of the 940th Hospital of Joint Logistic Support Force of Chinese People's Liberation Army and placed on EN via a nasogastric or nasointestinal tube from March 1, 2020, to October 30, 2021. The study was approved by the Ethics Committee of the 940th Hospital and was registered in the Chinese Clinical Trial Registry (Registration no.: ChiCTR-DOD-16008532). Informed consent was obtained from all participants before the observation.

Inclusion criteria were being aged >18 years, hemodynamically stable at the time of starting EN using a nasogastric or nasointestinal tube and providing consent for participation in this study. Exclusion criteria included patients who were pregnant, lost to follow-up during the 5 days of observation, and whose EN was suspended during observation for any reason except FI, such as surgery and special treatment. Patients were continuously observed for 5 days after EN commenced, based on the study by Gungabissoon *et al.*,[4] in which FI occurred after a median of 3 days after EN initiation. Figure 1 presents a flow diagram of the screening process for potential study participants.

Feeding protocol

The feeding protocol in our unit involved starting EN using a nasogastric or nasointestinal tube when patients were hemodynamically stable. A nurse inserted a 14-Fr silicone

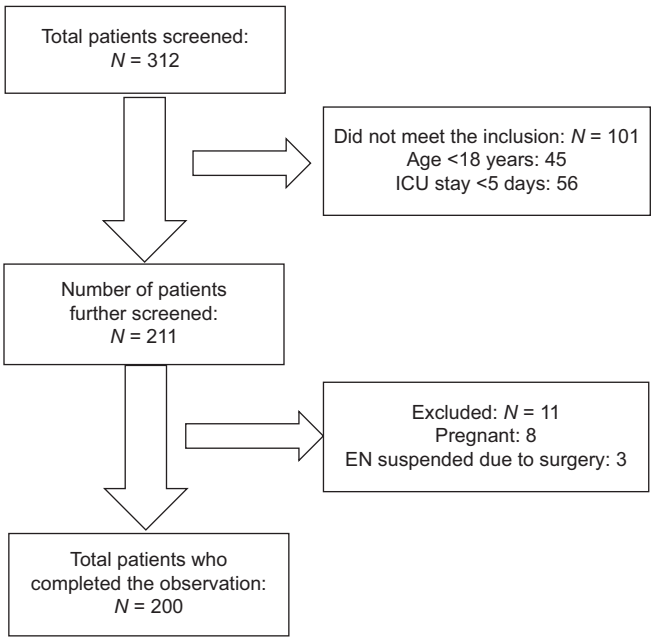

Figure 1: Patients included in the study. EN: Enteral nutrition, ICU: Intensive care unit

nasogastric tube or Ch-14 polyurethane nasointestinal tube at the beginning of feeding. A peristaltic pump was used to maintain a constant rate when patients were fed. The pumping speed was 25–50 mL/h at the beginning of the feeding and was increased by 10 mL/h every 8–12 hours in patients without FI.[10] The feeding goal was 25–30 kcal/kg/day,[11,12] and 1 mL of nutritional liquid contained 1–1.5 kcal energy. The temperature of the nutritional liquid was maintained at 35–40°C using the pump. Patients were cared for in a semi-recumbent position (i.e., the head of bed angle between 30° and 45°).[11,13]

Definitions

We consistently observed whether the patients had high gastric residual volume (GRV), abdominal pain, abdominal distention, vomiting, and diarrhea, as well as the feeding value for 5 days after EN was initially pumped. Based on the WGAP of the ESICM definitions, FI was identified as GRV ≥200 mL (measured by aspirating every 4 hours with a 50 mL syringe) or when patients vomited, diarrhea occurred, feeding was disrupted by abdominal distension and pain, or the feeding goal of at least 20 kcal/kg body weight/day could not be reached within 72 hours.[1] We used the WGAP of the ESICM criterion for defining gastrointestinal dysfunction. Vomiting (emesis) is the visible regurgitation of gastric content, irrespective of the amount.[1] Diarrhea was defined as three or more loose or liquid stools per day with a stool weight >200–250 g/day (or >250 mL/day). Abdominal distension was defined as a complaint of abdominal expansion or full abdominal distention resulting in EN suspension observed during an examination. Abdominal pain was noted to be present when a patient complained of abdominal pain and could not stand. FI score = abdominal distension/pain (0, 1, 2, or 5 points) + nausea/vomiting (0, 1, 2, or 5 points) + diarrhea (0, 1, 2, or 5 points).[2] The gastrointestinal dysfunction score consists of five categories: no risk, increased risk, gastrointestinal dysfunction, gastrointestinal failure, and life-threatening.[3]

Variables

Patients' characteristics and risk factors, including sex, age, general conditions (prolonged bedrest >3 days, postoperative within 1 day, multiple organ dysfunction, and sepsis), biochemical indexes (serum albumin, glucose, and potassium), gastrointestinal functions (abdominal surgery, fasting >3 days, severe pancreatitis, and gastrointestinal tract disease or injury), and treatment measures (the use of sedative and analgesic agents, invasive mechanical ventilation, and antacid agents) were recorded. Furthermore, severity indexes (Acute Physiology and Chronic Health Evaluation II [APACHE II],[14] Glasgow Coma Scale, Injury Severity Score,[15] and AGI grade) were calculated at the beginning of EN.[1]

Preventive treatments included the type of nutrition used (whole protein or short peptide), use of probiotics accompanied with EN (2 g *Bacillus bifidus* or 2 g *Bacillus subtilis* three times daily), albumin supplementation accompanied with EN (intravenous drip serum albumin 100 mL once daily), combined parenteral nutrition with the addition of glutamine in EN (2 g glutamine granules was added to 500 mL nutritional liquid), gastric motility drugs (5 mg mosapride or 10 mg domperidone three times daily), cathartic (100 mL rhubarb three times daily or 10 g polyethylene glycol 4000 powder two times daily), and early enemata (retention enema with 100 mL rhubarb three times daily or an enema with 110 mL glycerine) when patients had abdominal distention or constipation before EN. All preventive treatments were recorded at the beginning of EN.

Statistical analysis

Data are expressed as means ± standard deviations and rate (%). Categorical data were compared using the Pearson Chi-square test, depending on the sample size. The confidence intervals were determined, assuming the data had a binomial distribution. Continuous data were compared using the independent sample *t*-test and repeated measurement analysis of variance (Greenhouse–Geisser test when Mauchly's Test of Sphericity <0.1). Statistical significance was set at a *P* value <0.05 to account for multiple comparisons in the univariate risk factor analysis.

Multivariate analysis included logistic stepwise regression according to the Wald test. Data with a *P* value <0.05 included in the logistic equation were considered independent risk factors or preventive treatments. Missing values were addressed using an intentionality analysis (intention-to-treat), which means the individual missing data were supplemented with the corresponding data from the adjacent previous acquisition. All statistical calculations were performed using the SPSS software (version 19.0, IBM, USA).

RESULTS

Study population

We prospectively studied 200 critically ill patients who were fed EN via a nasogastric or nasointestinal tube [see the outline of the study in Figure 1]. This study included 131 males and 69 females with a mean age of 59.1 ± 17.8 years. The primary diagnoses for ICU admission

were trauma in 75 patients, alimentary system disease in 36 patients (severe pancreatitis, hemorrhage of the alimentary tract, and intestinal obstruction), cardiovascular system disease in 36 patients (hypertension, coronary disease, heart failure, and aneurysm), respiratory system disease in 23 patients (pulmonary infection, pneumonia, and chronic obstructive pulmonary disease), urinary system disease in 13 patients (renal failure and urinary stone), tumor and cancer in 7 patients, and miscellaneous in 10 patients.

The prevalence of feeding intolerance

FI was observed in 117 patients (58.5%) after a median EN duration of 2 days (mean: 2 ± 1.3 days; range: 1–5 days). The reasons for FI with a single symptom (gastrointestinal dysfunction score: no risk) included 39 cases of diarrhea, 36 cases with GRV ≥200 mL, 5 cases of vomiting, and 4 cases with abdominal distention. The reasons for double symptoms (gastrointestinal dysfunction score: increased risk) in FI included 17 cases with GRV ≥200 mL and diarrhea, 4 cases with GRV ≥200 mL and abdominal distention, 3 cases with GRV ≥200 mL and vomiting, 2 cases with GRV ≥200 mL and abdominal pain, and 2 cases with abdominal distention and diarrhea. The reasons for triple symptoms (gastrointestinal dysfunction score: gastrointestinal dysfunction) included three cases of GRV ≥200 mL, vomiting, and diarrhea and two cases of abdominal distention, vomiting, and diarrhea. In terms of the FI score, 77 cases had 1 or 2 points (1 point: 56; 2 points: 21), 10 cases had 3 or 4 points (3 points: 7; 4 points: 3), and 30 cases had ≥5 points (5 points: 17; 6 points: 1; 7 points: 1, 9 points: 1; 10 points: 8, 15 points: 2).

Risk factors for feeding intolerance

Table 1 shows a comparison of risk factors between patients with and without FI according to their characteristics. Patients with a high APACHE II score had a predominantly higher FI rate and were more likely to have hyperglycemia ($P < 0.05$). Compared with patients who did not develop FI after feeding, those who developed FI were more likely to have abdominal problems such as abdominal surgery, fasting >3 days, severe pancreatitis, gastrointestinal tract disease or injury, high AGI grade, and sepsis. Patients who used sedatives and analgesics and had prolonged bed rest for >3 days were also more likely to have FI ($P < 0.05$) [Table 1]. Independent risk factors for increased FI during EN were fasting for >3 days, a higher APACHE II score, and AGI grade I [Table 2].

Preventive treatments for feeding intolerance

Compared with patients who developed FI after tube feeding, patients who did not develop FI were more likely to use whole protein for nutrition and albumin supplements.

Table 1: Comparison of the risk factors and preventive treatments between patients with and without feeding intolerance

Variable	Without FI (*n*=83)	With FI (*n*=117)	*P*
Gender, male, *n* (%)	56 (67.47)	75 (64.10)	0.622
Age, years, mean (SD)	58.07 (19.31)	59.88 (16.67)	0.480
Risk factors			
APACHE II score, mean (SD)	15.95 (4.50)	18.58 (7.18)	0.007
GCS score, mean (SD)	11.45 (3.85)	12.18 (3.87)	0.187
ISS score, mean (SD)	8.29 (12.54)	5.84 (11.06)	0.146
ALB, g/L, mean (SD)	30.22 (5.44)	29.47 (6.44)	0.390
Serum glucose, mmol/L, mean (SD)	9.54 (3.37)	10.45 (3.04)	0.049
Serum potassium, mmol/L, mean (SD)	3.89 (0.52)	3.81 (0.52)	0.341
Prolonged bedrest >3 days, *n* (%)	36 (43.37)	88 (75.21)	<0.001
Postoperative within 1 day, *n* (%)	14 (16.87)	17 (14.53)	0.653
Surgery for abdominal, *n* (%)	0	21 (17.95)	<0.001
Fasting >3 days, *n* (%)	2 (2.41)	51 (43.59)	<0.001
Trauma, *n* (%)	39 (45.78)	36 (30.77)	0.020
Sever pancreatitis, *n* (%)	0	21 (17.95)	<0.001
Gastrointestinal tract disease or injury, *n* (%)	1 (1.20)	36 (30.77)	<0.001
Sepsis, *n* (%)	5 (6.02)	20 (17.09)	0.020
MODS, *n* (%)	12 (14.46)	26 (22.22)	0.168
AGI grade, n (%)			<0.001
AGI grade I	34 (40.96)	70 (59.83)	
AGI grade II	1 (1.21)	17 (14.53)	
AGI grade III	0	2 (1.71)	
Invasive mechanical ventilation, *n* (%)	66 (79.52)	93 (79.49)	0.996
Sedative and analgesic agents, *n* (%)	39 (46.99)	77 (65.81)	0.008
Antacid agents, *n* (%)	49 (59.04)	83 (70.94)	0.080
Preventive treatments			
Whole protein for nutrition, *n* (%)	67 (80.72)	49 (41.88)	<0.001
Early catharsis	43 (51.81)	25 (21.37)	<0.001
Early enema	64 (77.11)	31 (26.50)	<0.001
Early use of gastric motility drugs	28 (33.73)	10 (8.55)	<0.001
Albumin supplementation	39 (46.99)	31 (26.50)	0.003
Use of probiotics	21 (25.30)	18 (15.38)	0.081
Combined parenteral nutrition	15 (18.07)	29 (24.79)	0.259
Addition of glutamine	26 (31.33)	27 (23.08)	0.193

FI – Feeding intolerance; APACHE – Acute physiology and chronic health evaluation; GCS – Glasgow Coma Scale; ISS – Injury severity score; ALB – Serum albumin; MODS – Multiple organ dysfunction; AGI – Acute gastrointestinal injury; SD – Standard deviation

Patients with abdominal distention or computation who used catharsis, enema, or gastric motility drugs early before tube feeding had a lower FI rate [Table 1]. Independent preventive treatments for decreasing FI during EN involved using whole protein for nutrition and early use of enema and gastric motility drugs (administered when a patient experienced abdominal distention or constipation) [Table 2].

Outcome analysis

Figure 2 compares the volume of nutritional liquid at different times between those with and without FI.

On the first day, the FI group consumed a mean of 790.1 ± 364.1 mL (1–1.5 kcal/mL), which is <1200 kcal (based on an adult weighing 60 kg) nutritional liquid. The patients without FI consumed a mean of 1021.1 ± 418.5 mL liquid and 1357.9 ± 395.6 mL on the first and second days of feeding, respectively, which was higher than the baseline (20 kcal/kg body weight/day).[12] The volume of nutritional liquids consumed by the FI group was 1138.7 ± 531.4 mL on the third day, rising to a mean of 1220.2 ± 567.8 mL on the last day. The volume of nutritional liquid in patients without FI increased to 1633.5 ± 349.7 mL on the last day. Table 3 shows the volume of nutritional liquid consumed daily by the patients.

We further analyzed the effect of preventive treatments, which are the independent factors from the multivariate analysis in Table 2. There were 150 patients in the preventive treatment group (PT, which used whole protein for nutrition and enema or gastric motility drugs early), of whom 68 (45.3%) had FI; in the without preventive treatment group (without PT), 49 of the 50 patients (98.0%) patients had FI.

Figure 3 compares the nutritional liquid values on different days between the PT and without PT groups. Significant differences were observed between the PT and without PT groups ($F_{Between}$ = 38.33, P < 0.05). The PT group consumed a mean of 1266.5 ± 413.2 mL (1–1.5 kcal/mL) on the second day, which was higher than the baseline of 20 kcal/kg body weight/day (based on an adult weighing 60 kg, which is equal to 1200 mL nutritional liquid). Patients in the without PT group did not reach the baseline on the observational day (the highest volume of nutritional liquids consumed was 1192.2 ± 539.2 mL on the last day). Table 3 shows the volume of nutritional liquids consumed by the patients daily.

Figure 4 depicts a comparison of the FI and without FI patients during the survey based on the duration of invasive mechanical ventilation on different days. Invasive mechanical ventilation times were shortened in the without FI and FI patients, but the time of the without FI patients was significantly shorter than that of the FI patients ($F_{Between}$ = 5.661, P < 0.018). In the without FI group, the invasive mechanical ventilation duration was <10 hours on Days 4 and 5. Table 4 shows the duration of invasive mechanical ventilation used by the patients daily.

We also compared the differences in invasive mechanical ventilation duration between the PT and without PT

Table 2: Multivariate analysis of the factors for feeding intolerance in the study participants

Variable	Wald	*P*	OR	95% CI
Independent risk factors				
Fasting >3 days	13.566	0.000	30.250	4.929–185.643
APACHE II score	17.477	0.000	1.288	1.115–1.352
AGI grade	12.232	0.007		
AGI grade I	10.999	0.001	5.615	2.025–15.569
Independent preventive factors				
Whole protein for nutrition	8.317	0.004	0.178	0.055–0.576
Early enema	10.700	0.001	0.199	0.075–0.523
Early use of gastric motility drugs	16.036	0.000	0.038	0.008–0.188

APACHE – Acute physiology and chronic health evaluation; AGI – Acute gastrointestinal injury; OR – Odds ratio; CI – Continuous integration

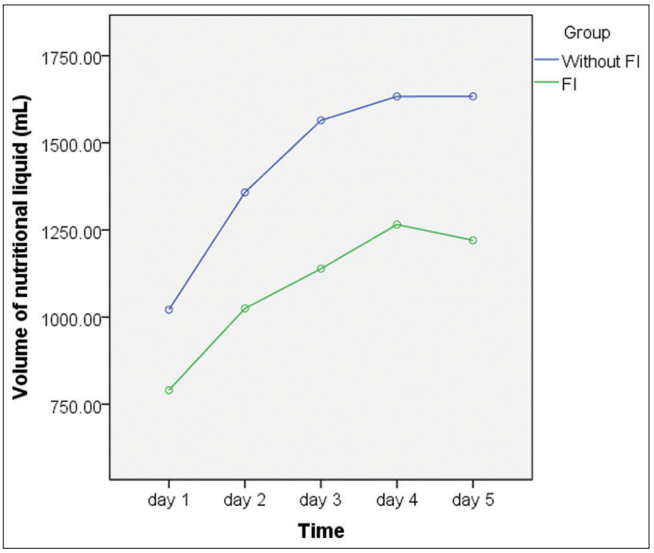

Figure 2: Comparison of the volume of nutritional liquid in different days between both groups

Table 3: Volume of the nutritional liquid on each day

Group	Time, mean (SD)					F_{Time}	$F_{Between}$	F_{Mutual}
	Day 1 (mL)	Day 2 (mL)	Day 3 (mL)	Day 4 (mL)	Day 5 (mL)			
Without FI (*n*=83)	1021.10 (418.49)	1357.88 (395.59)	1564.52 (384.92)	1633.06 (379.34)	1633.52 (349.73)	85.253	50.122	2.572
With FI (*n*=117)	790.08 (364.14)	1024.73 (434.74)	1138.73 (531.44)	1265.57 (608.09)	1220.21 (567.83)			
t/Z	4.153*	5.541*	−5.298#	−4.644#	−5.164#			
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.046
Without PT (*n*=50)	662.10 (324.90)	852.60 (411.09)	1024.92 (504.42)	1088.24 (585.65)	1192.20 (539.23)	59.394	38.33	1.834
With PT (*n*=150)	960.57 (399.84)	1266.45 (413.22)	1412.27 (488.94)	1528.03 (499.61)	1458.24 (510.46)			
t/Z	−4.776*	−6.141*	−4.813*	−5.157*	−3.147*			
P	0.000	0.000	0.000	0.000	0.002	0.000	0.000	0.133

*Independent-samples *t*-test *t* value; #Mann–Whitney *Z* value. FI – Feeding intolerance; PT – Preventive treatments; SD – Standard deviation

Table 4: The time of the invasive mechanical ventilation at each day

Group	Time					F_{Time}	$F_{Between}$	F_{Mutual}
	Day 1 (h), mean (SD)	Day 2 (h), mean (SD)	Day 3 (h), mean (SD)	Day 4 (h), mean (SD)	Day 5 (h), mean (SD)			
Without FI (*n*=83)	11.83 (9.82)	12.05 (9.71)	10.95 (9.96)	9.15 (10.04)	9.48 (10.30)	4.916	5.661	0.729
With FI (*n*=117)	13.56 (9.25)	14.44 (9.55)	14.00 (10.00)	13.06 (10.76)	12.19 (10.44)			
t/*Z*	−1.267*	−1726*	−2.127*	−2.321#	−1.820*			
P	0.207	0.086	0.035	0.020	0.070	0.003	0.018	0.526
Without PT (*n*=50)	15.34 (8.80)	15.96 (8.97)	15.54 (9.51)	15.63 (10.42)	13.93 (10.71)	2.679	9.227	0.756
With PT (*n*=150)	12.01 (9.62)	12.61 (9.76)	11.80 (10.11)	10.04 (10.34)	10.11 (10.22)			
t/*Z*	2.166*	2.143*	2.298*	3.307*	2.264*			
P	0.032	0.033	0.023	0.001	0.025	0.050	0.003	0.511

*Independent-samples *t*-test *t* value; #Mann–Whitney *Z* value. FI – Feeding intolerance; PT – Preventive treatments; SD – Standard deviation

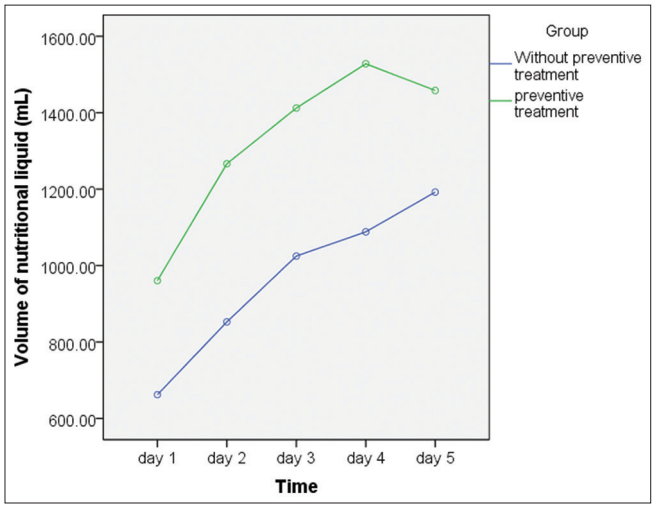

Figure 3: Comparison of the volume of nutritional liquid in the different days between the preventive treatment group and without preventive treatment group

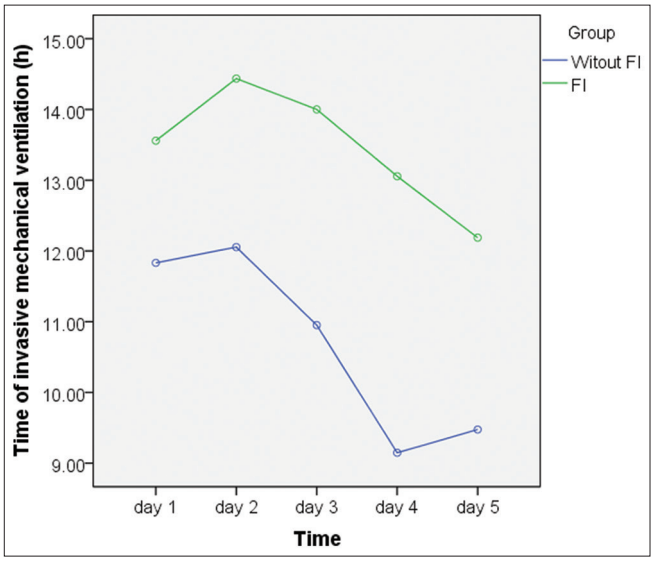

Figure 4: Comparison of the time of invasive mechanical ventilation in the different days between both groups

groups. Figure 5 shows the difference in invasive mechanical ventilation duration between the PT and without PT groups on each survey day. The invasive mechanical ventilation duration in the PT and without PT groups was shortened, but the duration in the PT group was significantly shorter than that in the without PT group ($F_{Between}$ = 9.227, $P < 0.003$).

DISCUSSION

In this prospective study of critically ill patients, we found that the prevalence of FI during EN was 58.5%, and that it occurred early with a median EN duration of 2 days (mean: 2 ± 1.3 days; range: 1–5 days). FI was especially more frequent in patients who had fasted for >3 days and had a high APACHE II score and AGI grade before EN. The most common reasons for FI in critically ill patients were diarrhea (33.33%) and GRV ≥200 mL (30.77%). The patients also developed FI for a combination of reasons, such as GRV ≥200 mL and diarrhea, or GRV ≥200 mL, vomiting, and diarrhea. Gastrointestinal symptoms are frequent in the ICU, with approximately 62% of patients exhibiting at least one gastrointestinal symptom for at least 1 day.[1,16] Moreover, the most common cause of FI is high GRVs, accounting for 61.6% of intolerant patients, followed by vomiting/emesis or diarrhea (36.6%).[1] Our results from ICU patients in a general hospital were consistent with those previously reported.

Based on the WGAP of the ESICM definition, FI is a general term indicating enteral feeding intolerance for various clinical reasons, meaning that there are numerous risk factors for FI.[1] Impaired digestive system function, including upper gastrointestinal tract dysfunction (gastric aspirates and vomiting) and lower gastrointestinal tract dysfunction (diarrhea and abdominal distension), can directly lead to FI. In our study, patients with high APACHE II scores had a predominantly higher rate of FI, as did patients with abdominal problems, such as abdominal surgery, fasting >3 days, severe pancreatitis, gastrointestinal tract disease or injury, and high AGI grade. Recently, a study demonstrated a high percentage of trauma patients with perturbed gastrointestinal motility, including

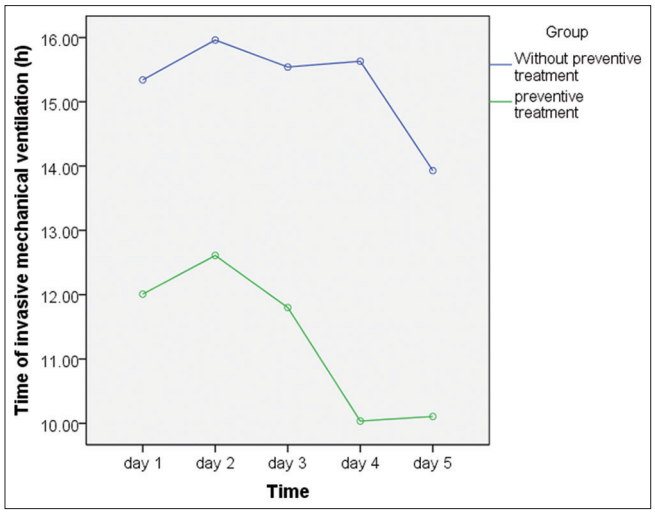

Figure 5: Comparison the time of invasive mechanical ventilation in the different day between the preventive treatment group and without preventive treatment group

nausea, vomiting, abdominal distension, constipation, diagnosed ileus, and elevated GRV.[17] We found that, in the trauma group, patients without severe pancreatitis and gastrointestinal injury were significantly less affected by FI than those with these conditions, which may explain why gastrointestinal injury in trauma patients was analyzed separately. Therefore, gastrointestinal injury has a more direct effect on FI. Patients with fasting of >3 days or prolonged bed rest (i.e., >3 days) were more prone to slow intestinal peristalsis, gastrointestinal mucosal atrophy, thinned or broken villi, and ultimately digestion and absorption barrier dysfunction.[18-20]

Patients who used sedatives and analgesics were also more likely to develop FI in our study. These drugs can act on relevant receptors in the gastrointestinal tract and reduce gastrointestinal excitatory neurotransmitter release, which may directly or indirectly inhibit gastrointestinal functions, ultimately inducing FI.[8,21-23] In our multivariate analysis, a higher APACHE II score, fasting >3 days, and AGI grade I before EN were independently associated with subsequent FI. This means that patients with severity indexes or abdominal problems before starting EN are at risk of FI.

Preventive treatments such as using whole protein for nutrition, albumin supplementation, and early use of catharsis, enema, and gastric motility drugs in patients with abdominal distention or constipation can decrease the rate of FI. In 2006, the ESPEN guidelines on EN suggested that whole protein formula, which results in a reduction in the incidence and/or frequency of diarrhea, is appropriate for most patients.[12] Compared to the whole protein, the short peptide is more likely to be a hyperosmotic EN formula that causes diarrhea.[14] Our results are consistent with the previous report that whole protein for nutrition can reduce the rate of FI. In 2016 and 2019, the Society of Critical Care Medicine, American Society for Parenteral and Enteral Nutrition, and ESPEN guidelines suggested that agents to promote motility, such as prokinetic medications, should be initiated in patients with a high risk of aspiration, where clinically feasible.[11,24] Our results show that early administration of catharsis, enema, and gastric motility drugs in patients with abdominal distention or constipation is an effective preventive treatment. In particular, we observed that the early use of an enema with rhubarb, a traditional Chinese medicine, had a good effect. In our multivariate analysis, the use of whole protein for nutrition and early use of enema and gastric motility drugs in patients with abdominal distention or constipation were independently associated with FI abatement. This means that the use of whole protein for nutrition, enema, and gastric motility drugs in patients who have abdominal distention or constipation before starting EN can be identified as effective preventive treatments for intolerance.

We observed that FI was associated with marked reductions in calorie delivery and longer invasive mechanical ventilation time. According to Gungabissoon *et al.*,[4] calorie adequacy in patients without FI was approximately 1.2 times that of patients with FI, and ventilator-free days in patients with FI were approximately four times that of patients without FI. Taken together, these data are consistent with the concept that FI contributes to poor outcomes.

We also compared the value of nutritional liquid and invasive mechanical ventilation duration on different days between the PT (early use of whole protein for nutrition and enema or gastric motility drugs) and without PT groups during the survey, showing that patients receiving preventive treatments experienced augmentation in calorie delivery and reduced invasive mechanical ventilation times. Preventive treatments with EN in critically ill patients effectively reduce the incidence of FI and contribute to better outcomes.

Limitations

This study has some limitations. Based on a previous study, we prospectively observed critically ill patients for 5 days after initial pumping of EN, resulting in an outcome analysis limit in the volume of nutritional liquid delivery and the time of mechanical ventilation. However, we did not analyze long-term prognostic indicators such as mortality. Therefore, randomized controlled trials are required to verify the effectiveness of the preventive measures.

CONCLUSION

This study found that FI during EN was frequent, occurred early, and had several risk factors; a higher APACHE II score, fasting >3 days, and AGI grade I before EN were independently associated with a high incidence of FI. Moreover, we identified that using whole protein for nutrition, enema, and gastric motility drugs in patients with abdominal distention or constipation before starting EN are effective preventive treatments that have significantly reduced the incidence of FI and contributed to better outcomes.

Ethical considerations

The study was approved by Ethics Committee of the 940th Hospital of Joint Logistic Support Force of Chinese People's Liberation Army, China, and was registered in the Chinese Clinical Trial Registry (Registration no.: ChiCTR-DOD-16008532). Informed consent was obtained from all participants before the observation. The study adhered to the principles of Declaration of Helsinki, 2013.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available but can be obtained from the corresponding author on reasonable request.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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