BMC Gastroenterology

SYSTEMATIC REVIEW

Open Access

Risk factors for enteral feeding intolerance in critically ill patients: an updated systematic review and meta-analysis

Si Wang[1†], Yang He[2†], Jing Yi[3] and Liyan Sha[4*]

Abstract

Background This meta-analysis aimed to evaluate the factors influencing enteral nutrition feeding intolerance in critically ill patients.

Methods PubMed, Embase, Scopus, Medline, Web of Science, CNKI, VIP, WanFang and CBM databases were searched. A sensitivity analysis was carried out to explore the influence of individual studies on the pooled results of the included studies using a fixed-effects model or a random-effects model. The pooled results were expressed as the odds ratios (ORs) and 95% confidence intervals (CIs). Finally, a funnel plot was developed to describe the publication bias.

Results Twenty-three studies involving 30,688 participants were included. Meta-analysis results showed that age, body mass index (BMI), APACHE II score, renal insufficiency, digestive system diseases, hypoproteinemia, sepsis, and post-pyloric feeding, starting feeding within 48 h, feeding pattern, nutritional formula, sedative drugs, vasoactive drugs, use of more than two antibiotics, oral potassium preparation, mechanical ventilation, days of mechanical ventilation, length of ICU stay, and mortality were the influencing factors of enteral nutrition feeding intolerance in critically ill patients. The results of the sensitivity analysis showed that the direction of the pooled effect size did not change after excluding each study one by one, suggesting that the results of the meta-analysis were robust.

Conclusions According to the influencing factors, medical staff can pay attention to the high-risk patients at ICU admission to reduce the risk of feeding intolerance.

Keywords Nutrition, Nursing, Enteral feeding intolerance, Risk factors, Meta-analysis

Background

The intensive care unit (ICU) is a core unit for the treatment of critically ill patients. Patients admitted to the ICU often have a decreased level of consciousness due to severe trauma, multiple organ dysfunction or sepsis and other pathological states. About 60%-80% of the patients have dysphagia or impaired gastrointestinal function, and independent feeding is not sufficient to meet their nutritional needs [1]. Studies have shown that the incidence of malnutrition in ICU patients is as high as 38%-78%, and nutritional status is significantly negatively correlated with the risk of infection, mechanical ventilation time and mortality

†Si Wang and Yang He these authors contributed equally to this work and should be considered as co-first authors.

*Correspondence:
Liyan Sha
479662368@qq.com
[1] Interventional Surgery Center, The Second Hospital of Dalian Medical University, Dalian, Liaoning 116000, China
[2] School of Nursing, Dalian Medical University, Dalian, Liaoning 116000, China
[3] Hand and Foot Surgery, The Second Hospital of Dalian Medical University, Dalian, Liaoning 116000, China
[4] Nursing Department, The Second Hospital of Dalian Medical University, 467 Zhongshan Road, Shahekou District, Dalian, Liaoning 116000, China

[2]. Therefore, enteral nutrition (EN) is widely used as the preferred way of nutritional support in clinical practice, which provides proteins, carbohydrates and micronutrients to maintain intestinal barrier function and regulate immune function through nasogastric tube, nasointestinal tube or percutaneous endoscopic gastrostomy [3]. Based on evidence-based medical evidence, the 2022 clinical practice guidelines of the American Society for Parenteral and Enteral Nutrition (ASPEN) have clearly proposed [4] that in critically ill patients with hemodynamic stability, EN should be started as soon as possible after they admit to the ICU. However, the implementation of EN is often accompanied by a variety of complications, among which enteral feeding intolerance (EFI) has attracted much attention due to its high incidence of about 30.5%-65.7% and its significant impact on prognosis [5]. EFI is not only manifested as gastrointestinal symptoms such as gastric retention, vomiting, and diarrhea, but also regarded as a biomarker of disease severity. EFI is closely related to adverse outcomes such as an increased incidence of ICU-acquired myasthenia, an increased risk of ventilator-associated pneumonia, and increased 28-day mortality [6]. At present, there is no unified definition for EFI in the international medical community. The diagnostic framework proposed by the European Society of Critical Care Medicine (ESICM) in 2012 is the most widely used in clinical practice, which covers three dimensions [7]: (i) Gastrointestinal intolerance symptoms (gastric residual volume > 500 mL/24 h, vomiting ≥ 1 time/day or diarrhea > 3 times/day); (ii) Inadequate energy intake (actual intake < 80% of target requirement for 3 days); (iii) Forced interruption of EN for ≥ 48 h.

However, over the past 15 years, research in this field has been scarce. Existing reports are mostly observational studies in a single medical center, and there is no comprehensive systematic review of the influencing factors of EFI in critically ill patients. Therefore, this study aimed to find out the influencing factors of EFI early from demographic characteristics, disease severity, drug use, EN and nursing outcomes, so as to help identify critically ill patients at a high risk of EFI earlier and accurately in clinical work.

Methods

This research was reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [8]. The study protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024507865).

The PICO criteria for this article were as follows:

P (Population): Critical illness patients, who received EN support.

I (Intervention): Patients in the intervention group received EN, which referred to the way of nutritional support through the gastrointestinal tract, including oral or tube feeding [3].

C (Comparison): There may be no specific control here because the meta-analysis focused on identifying risk factors. However, patients who developed feeding intolerance could be compared with controls who did not develop feeding intolerance.

O (Outcome): The outcome was the occurrence of feeding intolerance, which usually referred to a series of gastrointestinal symptoms [5], such as gastric retention, vomiting, abdominal pain, diarrhea, and abdominal distension, and the interruption of EN or other changes in clinical gastrointestinal nutrition management caused by these symptoms.

Literature search strategy

PubMed, Web of Science, Embase, Cochrane Library, Scopus, China National Knowledge Infrastructure, VIP network, WanFang Data, and Chinese Biomedical Literature Database were searched for studies on the influencing factors of EFI in EN from the establishment of each database up to January 2024. The subject words and free words were combined for the literature search. The search strategy for PubMed is detailed in Supplementary Material 1.

Eligibility criteria

Inclusion criteria were as follows: (1) the original studies must explore the influencing factors of EFI in critical patients; (2) the participants were critically ill patients aged ≥ 18 years, with no restrictions on gender or race. (3) the outcome measure was the risk factors for EFI.

The following studies were excluded: (1) studies with abstracts but with no full texts, making it unable to extract data; (2) studies in which data were not complete or could not be converted; (3) studies in which the outcome indicators were inconsistent.

Data extraction and quality assessment

Literature was screened by two investigators based on the inclusion and exclusion criteria, and they cross-checked the results. In case of disagreement, a third investigator assisted in reaching a consensus. The following data were extracted: name of the first author, year of publication, country, type of study design, sample size, form of EFI presentation, and influencing factors (including age, gender, body mass index [BMI], APACHE II score, renal insufficiency, digestive system diseases, hypoproteinemia,

sepsis, post-pyloric feeding, start time of feeding, feeding pattern, nutritional formula, sedative drugs, vasoactive drugs, antibiotics, gastric kinetic drugs, oral potassium suppressants, mechanical ventilation, days of mechanical ventilation, days of ICU stay, and mortality). The quality of cohort studies was assessed using the Newcastle–Ottawa Scale (NOS) [9]. The tool contains eight items to judge the quality of the included studies, with a total score of 9 points. Studies with a score of 0 to 3 were considered low quality; studies with a score of 4 to 6 were deemed to have moderate quality, and 7 to 9 points denoted high quality. The scoring results are detailed in Supplementary Material 2. The quality of cross-sectional studies was assessed by using the scale recommended by the Agency for Healthcare Research and Quality (AHRQ) [10], including 11 items. Each item was evaluated as "yes", "no" or "unclear", where a "yes" scored 1 point, and a "no" or "unclear" scored 0 points. The scores of all items were added up to obtain the total score. A total score of 0–3 was defined as low quality, 4–7 as medium quality, and 8–11 as high quality. The scoring results are detailed in Supplementary Material 3. After the literature quality evaluation was completed, only studies of medium and high quality were included in the meta-analysis.

Statistical methods

RevMan 5.4 software was used for meta-analysis. Dichotomous variables were expressed as odds ratio (OR). The weighted mean difference (WMD) was used as the effect size for continuous variables. Each effect size was provided with a 95% confidence interval (CI). The heterogeneity among the included studies was analyzed (the test level was $\alpha = 0.1$), and the degree of heterogeneity was quantitatively determined. If there was no statistical heterogeneity and I^2 was less than 50%, the fixed-effects model was used for meta-analysis. If there was statistical heterogeneity among the studies, sensitivity analysis was performed to identify the source of heterogeneity by removing the included studies one by one. After excluding the influence of obvious clinical heterogeneity, the random-effects model was used for meta-analysis if I^2 was greater than 50%.

Ethics statement

Since our study exclusively performed secondary data analysis, ethical approval was not required.

Results

General information of the included studies

A total of 8,925 relevant records were searched from databases. 23 studies were finally included [11–33], involving 14 cohort studies [11–13, 15, 17, 20–23, 26, 27, 29, 31, 33], and 9 cross-sectional studies [14, 16, 18, 19, 24, 25, 28, 30, 32]. The detailed results of the literature quality evaluation are provided in Supplementary Material 2–3.

The flow chart of literature screening is shown in Fig. 1, and the general characteristics of the included studies are detailed in Supplementary Material 4–5.

Results of data analysis

Ten articles [11, 12, 17–19, 23, 24, 27, 29, 33] reported the relationship between age and EFI. Statistical heterogeneity was observed between studies ($P < 0.01$, $I^2 = 80\%$), and the I^2 was reduced to 59% after excluding the study by Ren in 2018 in the sensitivity analysis. The random-effects model was used for data analysis. A statistically significant difference was observed (WMD = -1.62, 95%CI: -2.71–0.52, $P = 0.004$), as shown in Figs. 2 and 3.

Five articles [12, 17, 19, 23, 27] reported the relationship between BMI and EFI, and statistical heterogeneity was observed between studies ($P < 0.01$, $I^2 = 70\%$). After the study by Murthy in 2022 [27] was excluded in the sensitivity analysis, the I^2 was reduced to 0. The data analysis was performed utilizing a fixed-effect model. The results showed a statistically significant difference (WMD = 0.04, 95%CI: 0.00–0.07, P = 0.03), as shown in Figs. 4 and 5.

Seven articles [12, 17, 19, 23, 24, 29, 33] reported the relationship between APACHE II score and EFI. Statistical heterogeneity was observed between studies ($P < 0.01$, $I^2 = 20\%$). The meta-analysis was conducted using the fixed-effects model. The difference was statistically significant (WMD = 0.86, 95%CI: 0.61- 1.10, $P < 0.00001$), as shown in Fig. 6.

Three articles [17, 19, 33] reported the relationship between renal insufficiency and EFI. Statistical heterogeneity was found between studies ($P = 0.10$, $I^2 = 56\%$), and the random-effects model was adopted. A statistically significant difference was noted (OR = 1.87, 95%CI: 1.05-3.33, $P = 0.03$), as shown in Fig. 7.

Six articles [12, 15, 18, 19, 23, 27] reported the relationship between digestive system diseases and EFI. Statistical heterogeneity was observed between studies ($P = 0.83$, $I^2 = 0$), and the fixed-effects model was utilized. The results revealed a statistically significant difference (OR = 1.36, 95%CI: 1.24 -1.49, $P < 0.00001$), as shown in Fig. 8.

Two articles [19, 27] reported the relationship between hypoproteinemia and EFI, and statistical heterogeneity was found between studies ($P = 0.32$, $I^2 = 0$). The fixed-effects model was adopted for data analysis. The results showed a statistically significant difference (WMD = -0.63, 95%CI: -1.01—-0.25, $P = 0.001$), as shown in Fig. 9.

Seven articles [12, 19, 23, 24, 27, 29, 33] reported the relationship between sepsis and EFI. Statistical

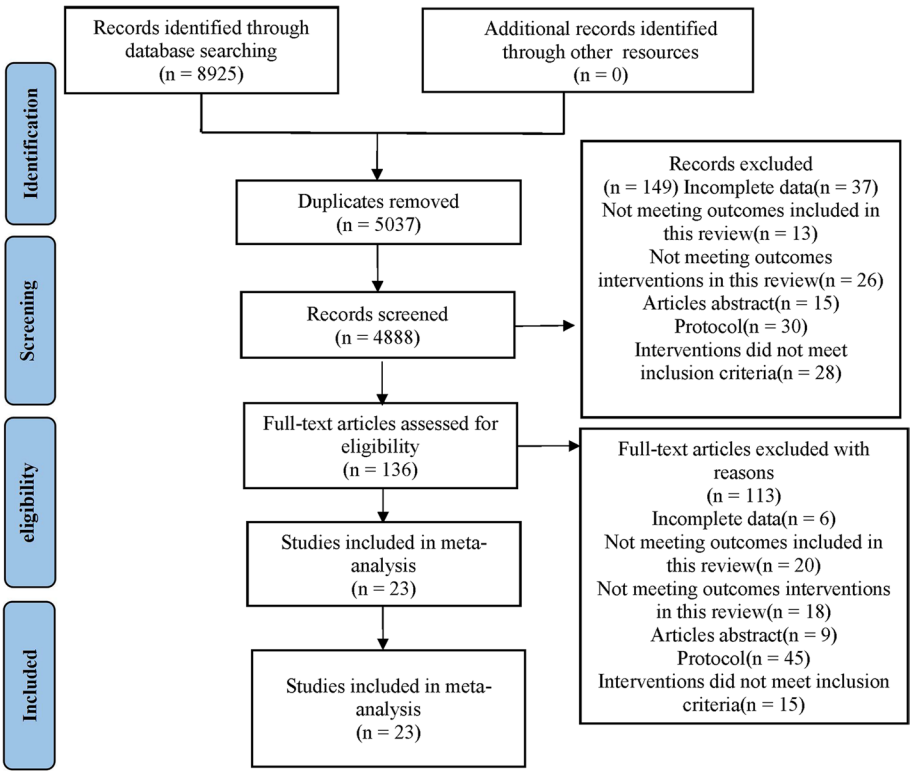

Fig. 1 Flow chart of literature screening

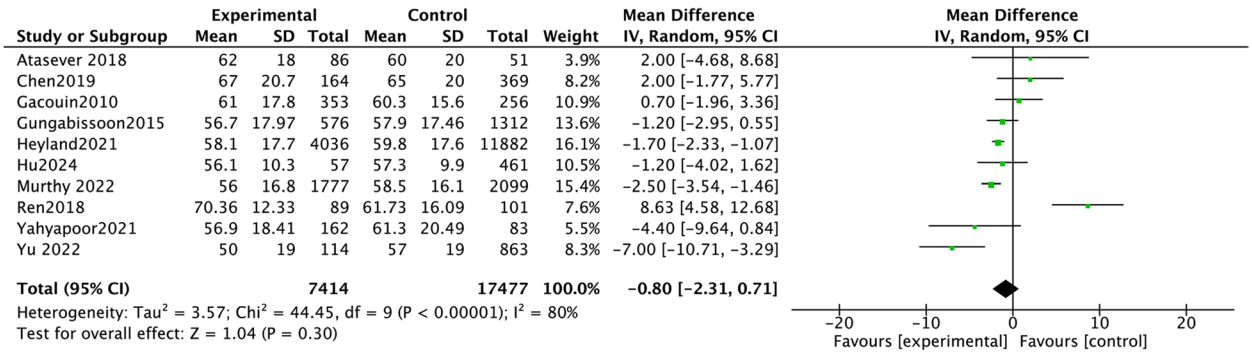

Fig. 2 The relationship between age and EFI

heterogeneity was observed between studies ($P=0.33$, $I^2=13\%$), and the meta-analysis was performed using the fixed-effects model. The results indicated a statistically significant difference (OR = 1.25, 95%CI: 1.14–1.37, $P<0.0001$), as shown in Fig. 10.

In terms of enteral feeding, eight articles [13–16, 18, 19, 27, 30] reported the relationship between postpyloric feeding and EFI. Statistical heterogeneity was found between studies ($P=0.33$, $I^2=79\%$), and the I^2 was reduced to 69% after the study by Zhang in 2023 was excluded [32]. We used the random-effects model for data analysis. A statistically significant difference was found (OR = 0.48, 95%CI: 0.32–0.74, $P=0.0007$), as shown in Figs. 11 and 12.

Six articles [14, 16, 18, 19, 25, 30] reported the relationship between starting EN within 48 h and EFI. There was statistical heterogeneity among the studies ($P<0.05$, $I^2=95\%$), and the I^2 was not significantly reduced after excluding each study in sensitivity analysis. According to the results of the subgroup analysis, a statistically

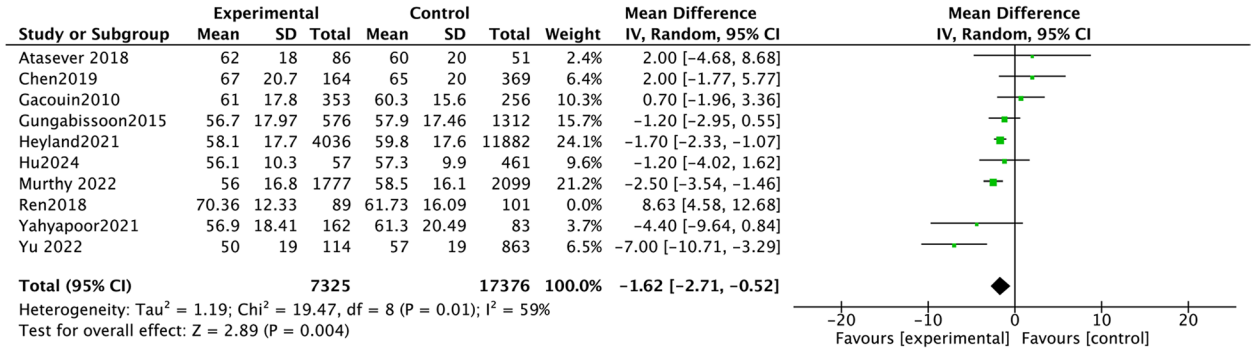

Fig. 3 The relationship between age and EFI

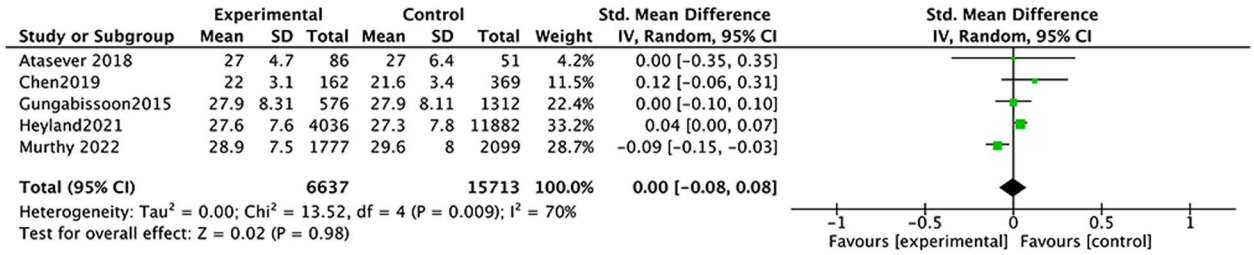

Fig. 4 The relationship between BMI and EFI

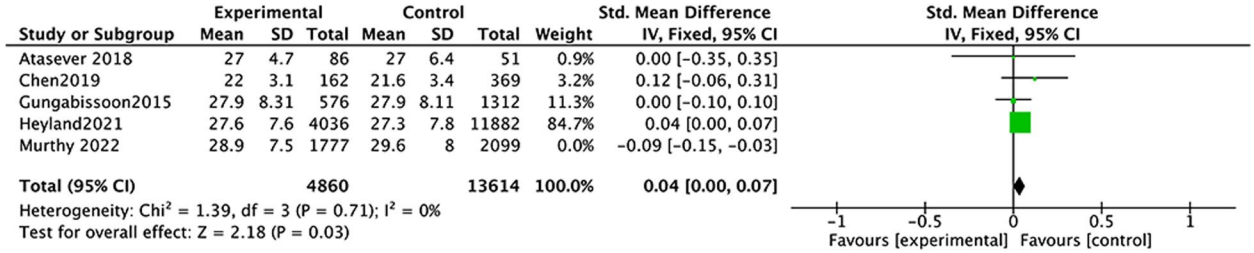

Fig. 5 The relationship between BMI and EFI

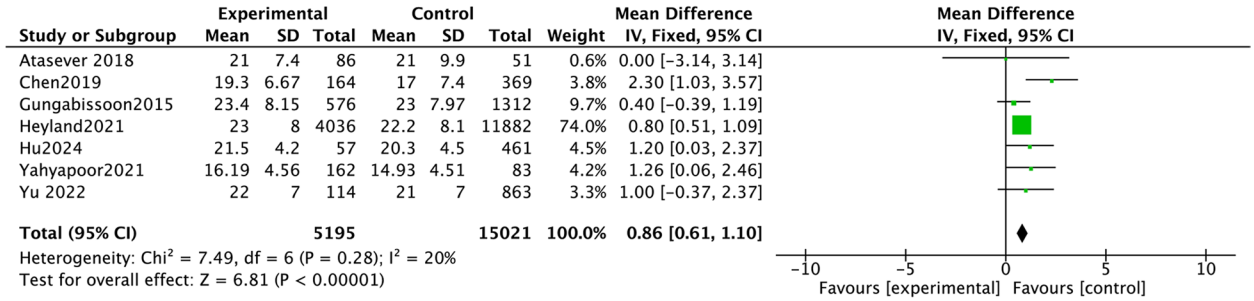

Fig. 6 The relationship between APACHE II score and EFI

significant difference was observed in the internal medicine group (OR = 0.4, 95%CI: 0.31–0.51, $P < 0.00001$), as shown in Figs. 13 and 14.

Four articles [19, 26, 27, 31] reported the relationship between EN patterns and EFI. Statistical heterogeneity was found between studies ($P = 0.15$, $I^2 = 43\%$), and the

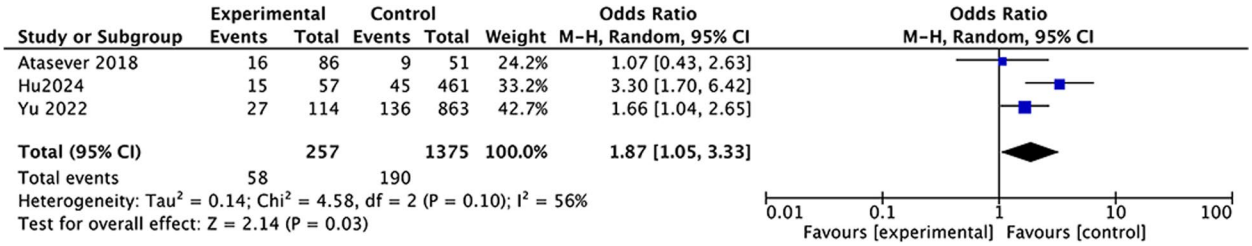

Fig. 7 The relationship between renal insufficiency and EFI

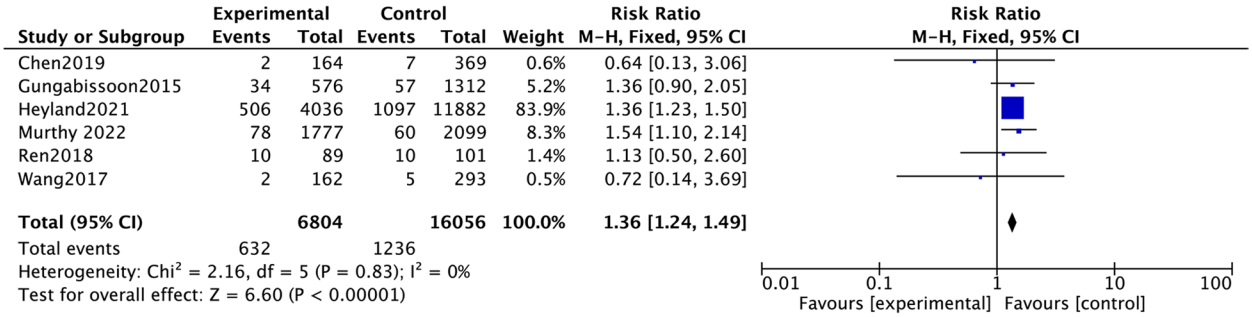

Fig. 8 The relationship between digestive system diseases and EFI

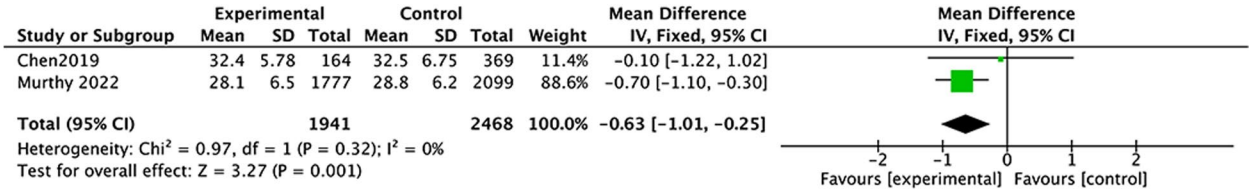

Fig. 9 The relationship between hypoproteinemia and EFI

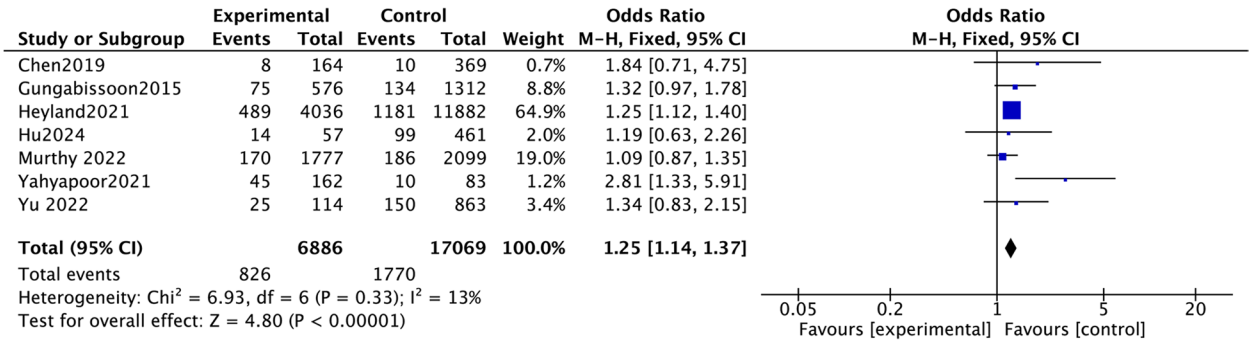

Fig. 10 The relationship between sepsis and EFI

I^2 was reduced to 31% after the study by Murthy in 2022 was excluded in the sensitivity analysis. The fixed-effects model was used for meta-analysis. The results showed a statistically significant difference (OR = 1.46, 95%CI: 0.99–2.16, $P = 0.05$), as shown in Figs. 15 and 16.

Two articles [12, 23] reported the relationship between nutritional formula and EFI. Statistical heterogeneity was found between studies ($P = 0.18$, $I^2 = 45\%$), and a fixed-effects model was adopted for data analysis. the difference was statistically significant

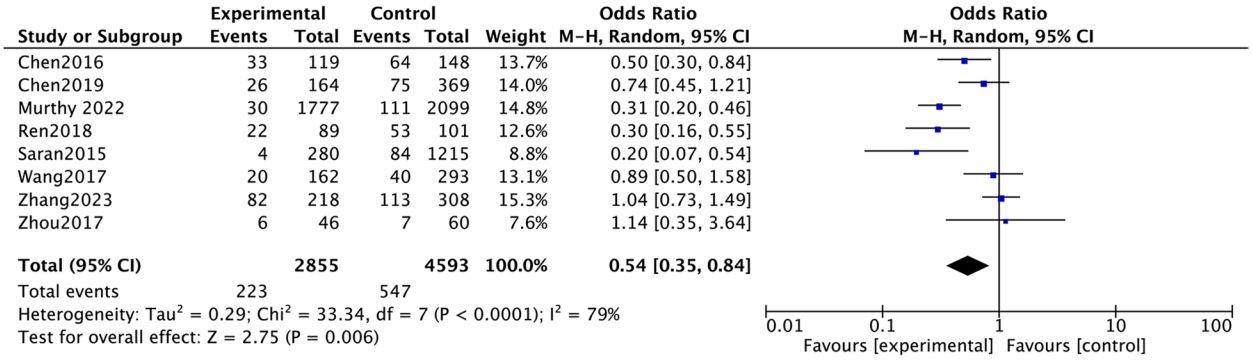

Fig. 11 The relationship between post-pyloric feeding and EFI

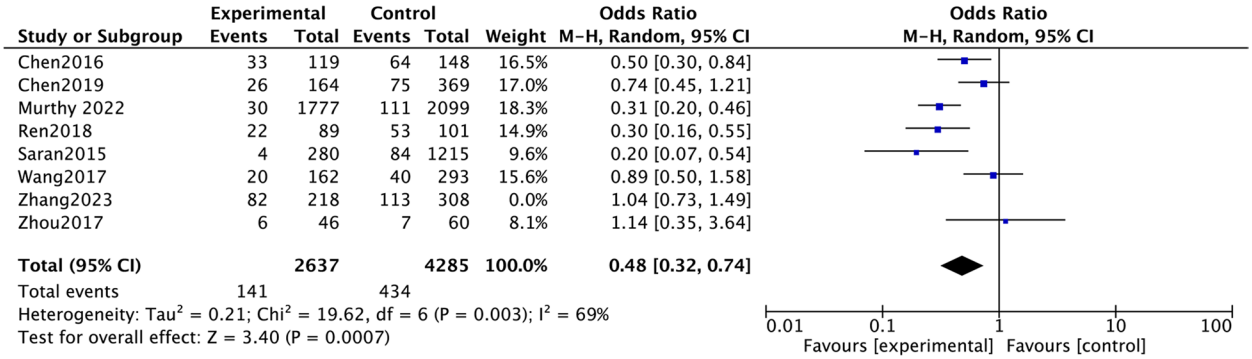

Fig. 12 The relationship between post-pyloric feeding and EFI

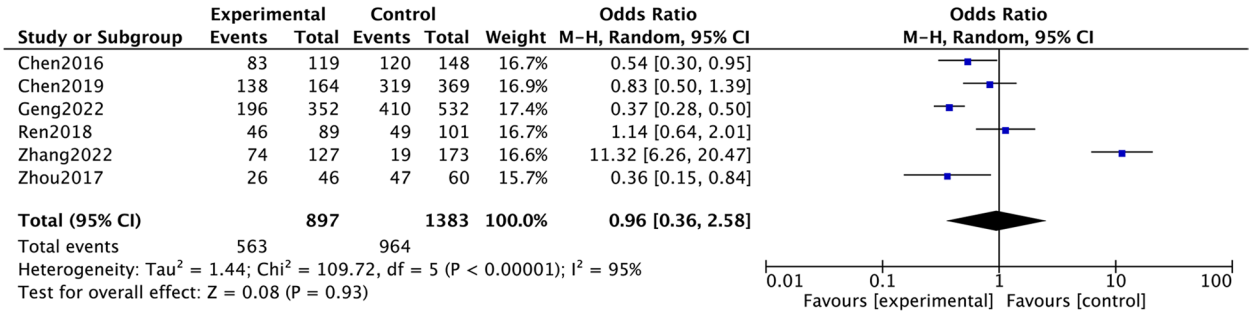

Fig. 13 The relationship between the starting EN within 48 h and EFI

(WMD = -7.27, 95%CI: -8.16—-6.36, $P < 0.00001$), as shown in Fig. 17.

In terms of drug use, eight articles [16–18, 25, 29, 30, 32, 33] reported the relationship between the use of sedatives and EFI. Statistical heterogeneity was found between studies ($P = 0.07$, $I^2 = 47\%$), and the meta-analysis was performed using the fixed-effects model. A statistically significant difference was found (OR = 1.68, 95%CI: 1.44–1.97, $P < 0.00001$), as shown in Fig. 18.

Eight articles [16–19, 21, 25, 27, 32] reported the relationship between the use of vasoactive drugs and EFI. Statistical heterogeneity was found between studies ($P < 0.01$, $I^2 = 76\%$), and the I^2 was reduced to 26% after the study by Zhang in 2023 was excluded [32]. The fixed-effects model was used, and the results showed a statistically significant difference (OR = 2.20, 95%CI: 1.93–2.51, $P < 0.00001$), as shown in Figs. 19 and 20.

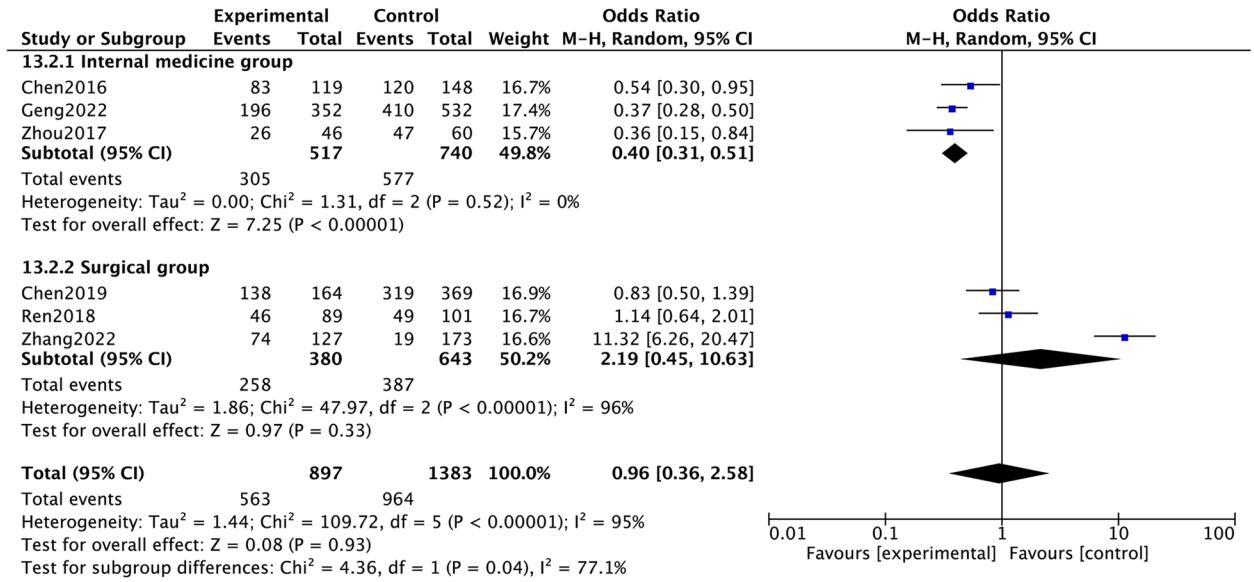

Fig. 14 The relationship between the starting EN within 48 h and EFI

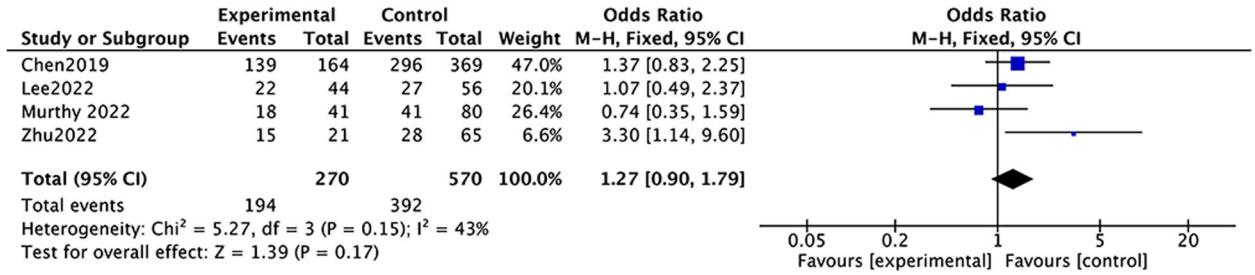

Fig. 15 The relationship between EN patterns and EFI

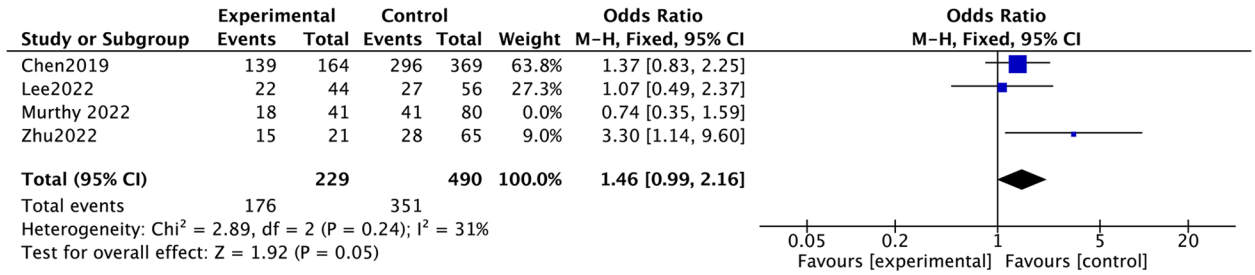

Fig. 16 The relationship between EN patterns and EFI

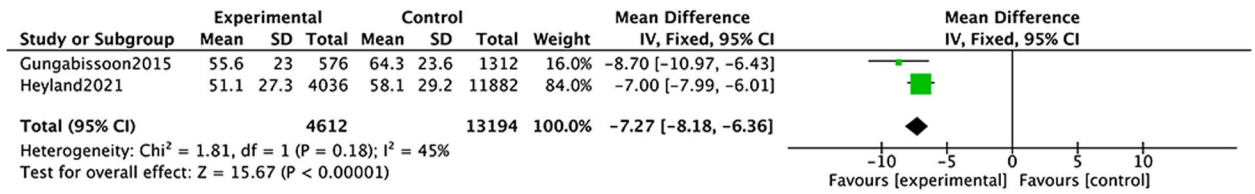

Fig. 17 The relationship between nutritional formula and EFI

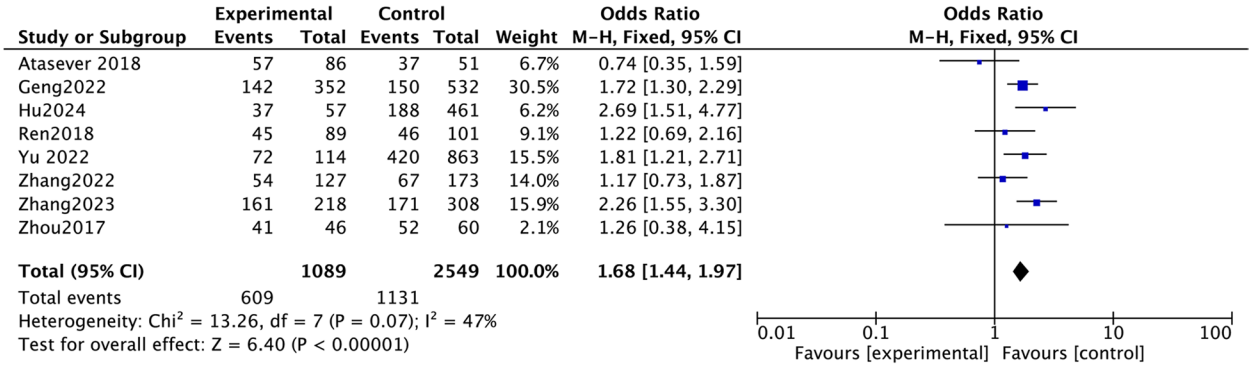

Fig. 18 The relationship between the use of sedatives and EFI

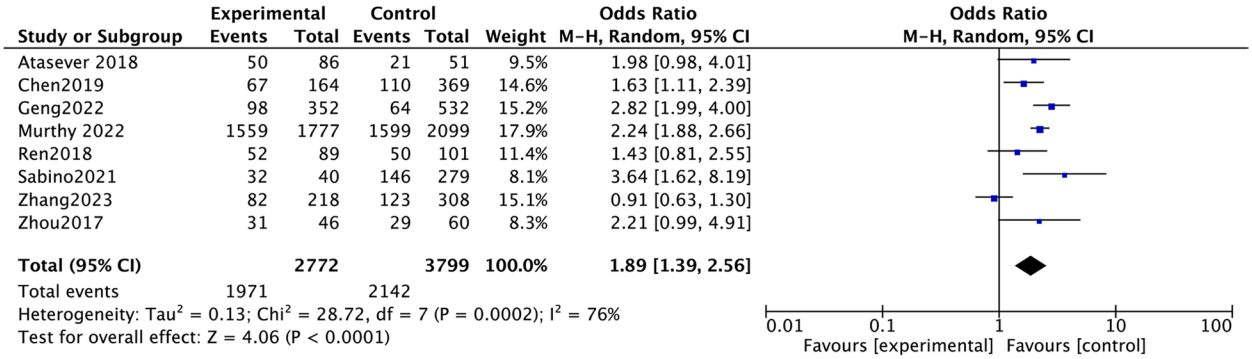

Fig. 19 The relationship between the use of vasoactive drugs and EFI

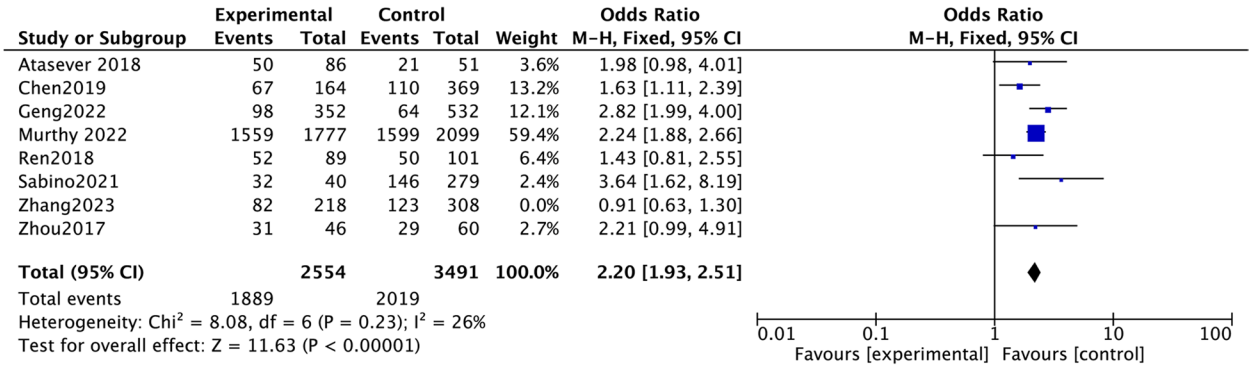

Fig. 20 The relationship between the use of vasoactive drugs and EFI

Five articles [16, 22, 25, 28, 32] reported the relationship between the use of more than 2 antibiotics and EFI. Statistical heterogeneity was found between studies ($P=0.16$, $I^2=40\%$), and the fixed-effects model was adopted. The difference was statistically significant (OR = 2.18, 95%CI: 1.85–2.58, $P<0.00001$), as indicated in Fig. 21.

Three articles [16, 25, 32] reported the relationship between the oral administration of potassium preparation agents and EFI, and statistical heterogeneity was observed between studies ($P<0.01$, $I^2=92\%$). After each study was excluded one by one in sensitivity analysis, there was no significant decrease in I^2. The random-effects model was utilized for analysis, and a statistically significant difference was noted (OR = 4.28, 95%CI: 1.73–10.59, $P=0.002$), as shown in Fig. 22.

Ten articles [16, 18, 19, 22, 25, 28–30, 32, 33] reported the relationship between mechanical ventilation and EFI,

and statistical heterogeneity was found between studies ($P=0.32$, $I^2=13\%$). The fixed-effects model was used for analysis. The results showed a statistically significant difference (OR = 1.98, 95%CI: 1.73–2.28, $P<0.00001$), as shown in Fig. 23.

Three articles [11, 19, 24] reported the relationship between the days of mechanical ventilation and EFI, and statistical heterogeneity was observed between studies ($P<0.01$, $I^2=93\%$). After excluding each study in sensitivity analysis, we found that there was no significant decrease in I^2. The random-effects model was utilized for analysis, and a statistically significant difference was noted (WMD = 4.36, 95%CI: 0.99–7.73, $P=0.01$), as shown in Fig. 24.

Seven articles [11, 12, 17, 19, 23, 24, 33] reported the relationship between the length of ICU stay and EFI, and statistical heterogeneity was found between studies ($P<0.01$, $I^2=93\%$). After excluding the study by Hu in 2024 [33] in sensitivity analysis, we found that the I^2 was reduced to 51%. The random-effects model was leveraged, and a statistically significant difference was observed (WMD = 3.41, 95%CI: 2.60–4.22, $P<0.00001$), as shown in Figs. 25 and 26.

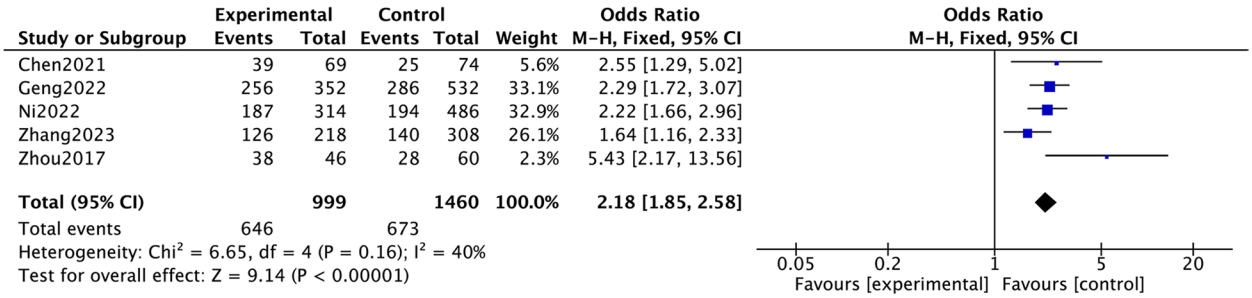

Fig. 21 The relationship between use of more than 2 antibiotics and EFI

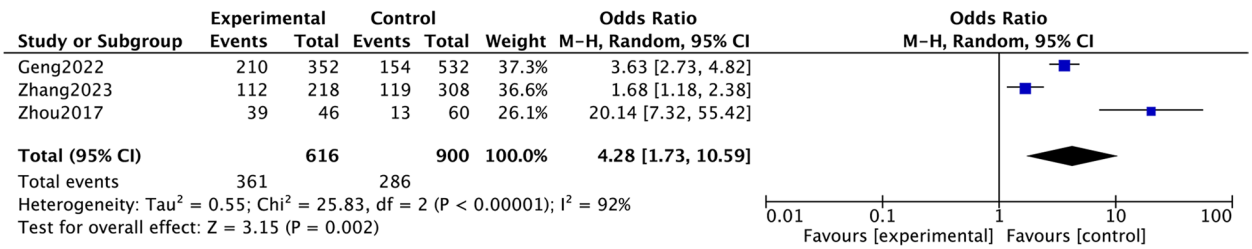

Fig. 22 The relationship between the oral administration of potassium preparation agents and EFI

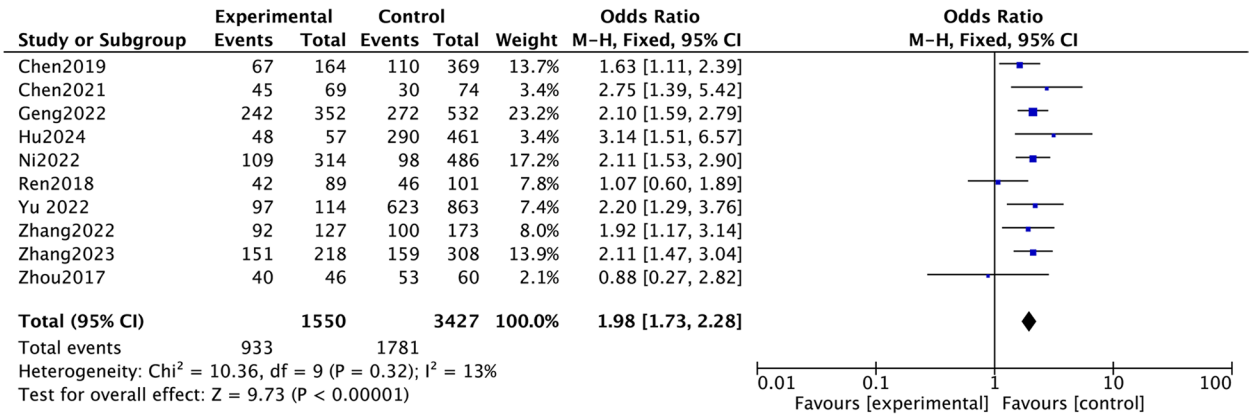

Fig. 23 The relationship between mechanical ventilation and EFI

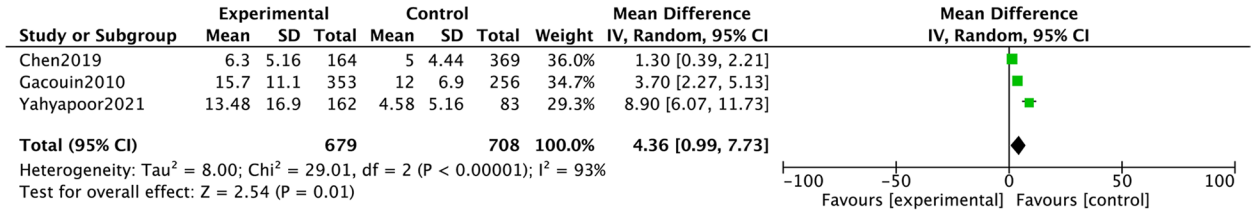

Fig. 24 The relationship between the days of mechanical ventilation and EFI

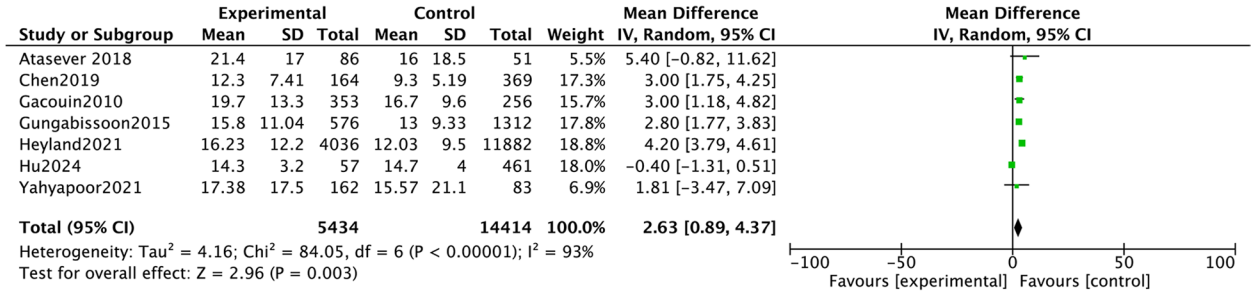

Fig. 25 The relationship between the length of ICU stay and EFI

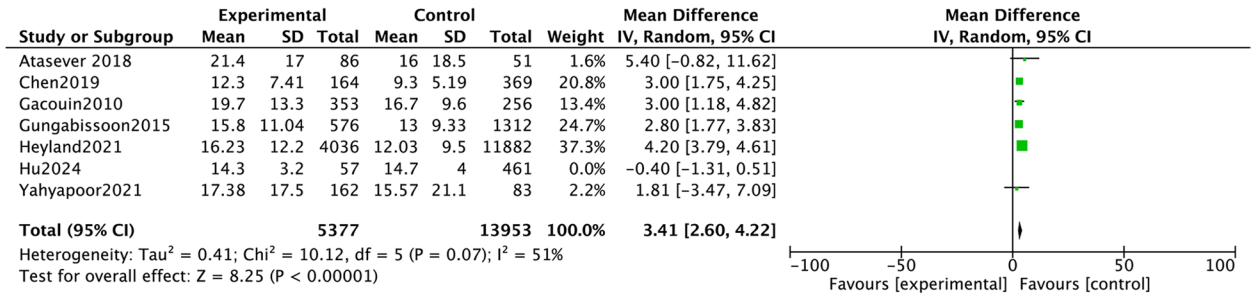

Fig. 26 The relationship between the length of ICU stay and EFI

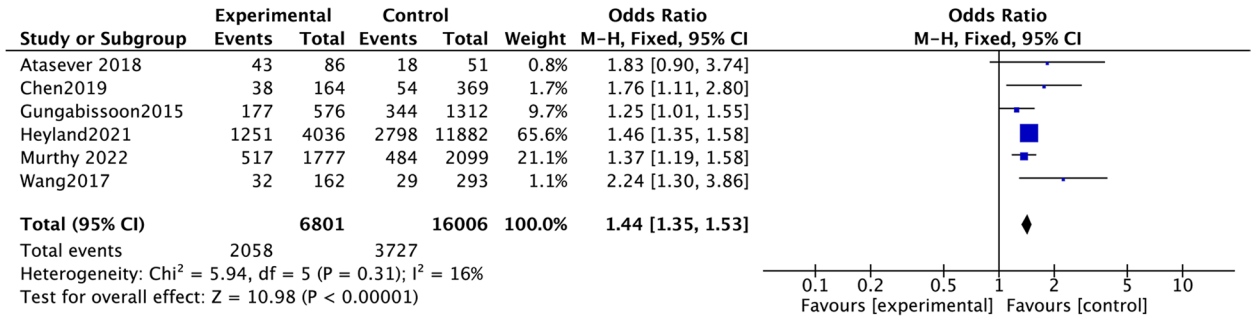

Fig. 27 The relationship between mortality and EFI

Six articles [12, 15, 17, 19, 23, 27] reported the association between mortality and EFI. Statistical heterogeneity was found between studies ($P=0.31$, $I^2=16\%$), and the fixed-effects model was used. A statistically significant difference was noted (OR = 1.44, 95%CI: 1.35–1.53, $P<0.00001$), as shown in Fig. 27.

The I^2 values for gender, respiratory disease, nervous system disease, cardiovascular disease, and gastric

motility drug use were 62%, 58%, 87%, 72%, and 97%, respectively. The I^2 did not decrease significantly after excluding each study one by one, and the *p*-value was not statistically significant.

Publication bias test

Since there were more than 10 included articles, a funnel plot was used to examine publication bias. The funnel plot was relatively symmetrical, indicating that there was a low possibility of publication bias, as shown in Fig. 28.

Discussion

Among the demographic characteristics of patients, age, BMI and APACHE II score were the influencing factors of EFI. The results of this study showed that age was negatively correlated with EFI. The average age of EFI patients was 1.62 years younger than that of non-EFI patients. This phenomenon may be explained by the imbalance between metabolic demand and nutritional supply. Young patients have a high basal metabolic rate, and intolerance is likely to occur if they fail to gradually adapt to their needs when starting EN [34]. The intensity of inflammatory response may be another reason. The inflammatory response to infection or trauma may be more severe in young adults, and inflammatory mediators directly inhibit gastrointestinal motility [35]. EFI monitoring should be focused on critically ill patients younger than 50 years old. A slower increasing rate of feeding (e.g., starting from 20 mL/h), combined with gastrointestinal motility drugs, can be considered. Furthermore, our results showed that BMI may be slightly positively correlated with the risk of EFI. Recent studies have suggested that obesity can change the distribution of normal intestinal flora and increase intestinal permeability [36], thereby increasing the occurrence of gastrointestinal intolerance such as diarrhea and constipation. APACHE II score is an important indicator to evaluate the severity of the patient's disease. A high APACHE II score indicates more serious conditions and enhanced stress responses in patients, which may severely damage gastrointestinal function and impair gastrointestinal tolerance [37, 38]. Patients with a high APACHE II score, especially those with a score above 20, should be considered as a high-risk group for EFI. Intestinal tolerance, gastric residual volume and abdominal distension score should be closely monitored during EN, and the risk of EFI should be comprehensively evaluated by intestinal ultrasound and other tools.

Disease severity, renal insufficiency, digestive system disease, hypoproteinemia and sepsis were significantly positively correlated with EFI. Recent studies [38] have shown that kidney disease can destroy the intestinal barrier, regulate the intestinal microbial composition and metabolism, and produce bioactive metabolites and toxins. Because patients themselves have stress-induced gastrointestinal injury in the gastrointestinal system, the risk of gastrointestinal dysfunction is greatly increased [38]. A study [39] has shown that hypoproteinemia is one of the important risk factors for EN-related diarrhea in critically ill patients, possibly because the decrease of plasma colloid osmotic pressure caused by hypoproteinemia leads to intestinal mucosal edema and intestinal villus malabsorption. On the other hand, hypoproteinemia causes an increase in the osmotic pressure difference

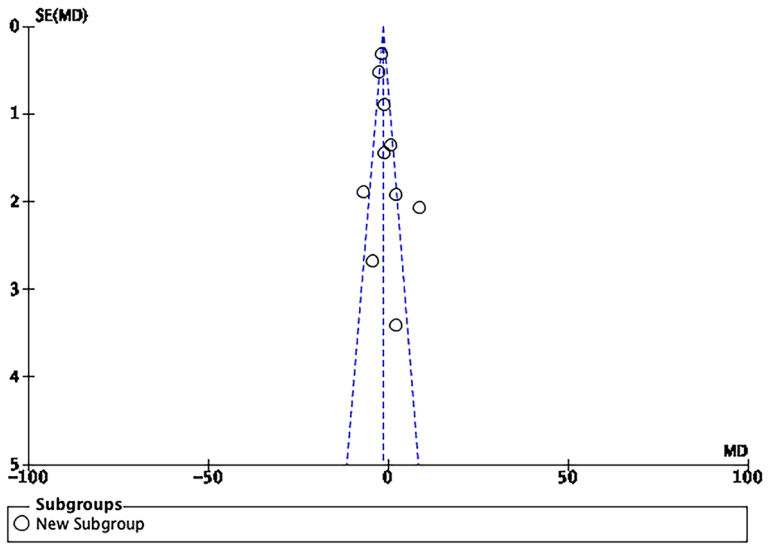

Fig. 28 Funnel plot of publication bias

between the blood vessels and the interstitial fluid, and a large amount of fluid penetrates into the intestinal cavity, leading to the imbalance of intestinal flora. Zhou et al. [16] also believed that the patient was prone to intestinal ischemia due to sepsis and was more likely to develop feeding intolerance during EN, including abdominal distension, diarrhea, vomiting and other symptoms.

According to the results of this study, starting feeding within 48 h, post-pyloric feeding, and feeding enough target calories showed a significant negative correlation with EFI and were protective factors for EFI. Nasointestinal tube feeding is less affected by the gastrointestinal tract [40]. For most critically ill patients with gastrointestinal dysfunction, nasointestinal tube feeding can not only improve the patient's tolerance to nutrient solution but also increase their absorption rate of nutrients. In a prospective cohort study, Acosta et al. [41] pointed out that when the same dose of EN solution was given, the incidence of intolerance symptoms such as vomiting and gastric residual volume was significantly reduced in patients receiving post-pyloric feeding. Therefore, the advantages of small bowel feeding should be fully recognized, and the proportion of nasointestinal tube feeding should be appropriately increased based on the patient's condition, to reduce nasogastric tube feeding intolerance in critically ill patients. In this study, the relationship between starting feeding within 48 h and EFI was significant [OR = 0.96 ($p < 0.05$)], but the heterogeneity was high ($I^2 = 95\%$). In subgroup analysis, we classified the studies by Chen 2016, Geng 2022 and Zhou 2017 as the medical ICU group. The studies by Chen 2019, Ren 2018 and Zhang 2022 were classified as the surgical ICU group. There was no heterogeneity in the medical ICU group ($I^2 = 0$). The results showed that early feeding was more significantly beneficial for critically ill patients in the medical ICU (OR = 0.4, 95%CI: 0.31–0.51, $P < 0.00001$), probably because most of the patients in medical ICU were older and frailer, had more underlying diseases, and were more sensitive to EFI. The 2017 expert guidelines [42] suggest that most critical patients should start EN within 48 h, except for critical patients in special conditions. According to the meta-analysis of Bakker OJ [43], patients who received EN within 24–48 h after admission to ICU were more likely to have a shorter duration of mechanical ventilator use and a reduced incidence of infection and EFI. Therefore, it is recommended that critically ill patients should receive EN support as soon as possible within 24–48 h after admission to ICU to restore gastrointestinal function. Longer fasting time of patients is more likely to lead to gastrointestinal mucosal atrophy and affect the absorption of nutrients. When critical patients have the indications for EN, EN should be implemented as soon as possible to promote the smooth progress of EN solution. In recent years, the feeding methods of EN have been increasingly investigated. This study shows that continuous feeding is a risk factor for EFI, that is, intermittent feeding is a protective factor for EFI. This finding is consistent with results reported in other studies. For instance, Zhu et al. [31] and Singer et al. [44] have confirmed that intermittent feeding can reduce aspiration and diarrhea, and lower the occurrence of FI in EN.

In terms of drug use, the use of sedatives, vasoactive drugs, more than 2 antibiotics, and oral potassium suppressors showed a significant positive correlation with EFI. Before and during EN, the use of sedatives and vasoactive drugs will affect the peristalsis of the digestive tract and cause gastric emptying disorder in critically ill patients, leading to gastric retention, nausea, vomiting and other gastrointestinal intolerance symptoms [45]. For patients receiving sedatives and vasoactive drugs, nursing staff should closely monitor their gastric residual volume. For patients with increased gastric residual volume, the doctor should be informed in time to avoid the occurrence of gastric retention and ensure the smooth infusion of EN. It has been shown that the irrational use of broad-spectrum antibiotics is a leading contributor to forintestinal flora imbalance in human gut [46]. The reason is that the excessive use of broad-spectrum antibiotics kills beneficial intestinal bacteria and disrupts the balance of host microecology. At the same time, it also causes the proliferation of drug-resistant strains in the intestines, exacerbating the disruption of intestinal biological barrier and impairing gastrointestinal function. Consequently, it increases the risk of feeding intolerance, such as diarrhea [47]. In clinical work, it is recommended to use antibiotics according to standardized protocols, control indications, advocate for rational utilization, and discourage indiscriminate combinations. Studies [48, 49] have reported that probiotics supplementation enhances the composition of human digestive tract flora, increase host health benefits, promote intestinal barrier function, facilitate enhanced tolerance of EN, and potentially rectifies antibiotic-induced imbalance in intestinal flora [50]. Our findings are consistent with the results reported by Wei Juan et al. [51], suggesting that the administration of potassium preparation is an independent risk factor for diarrhea. On the one hand, ICU patients are critically ill and exhibit poor nutritional intake, possibly leading to decreased serum potassium. In clinical practice, potassium chloride and potassium citrate for injection are often injected through feeding tubes or added to EN solution. When liquid drugs are mixed with EN formula, incompatibility may occur. On the other hand, potassium

preparations are hypertonic solutions, which not only have a strong stimulatory effect on the gastrointestinal tract, especially when the patient is fasting, but also cause a large amount of fluid to be retained in the intestinal lumen [52], thereby increasing the occurrence of EFI. Therefore, in clinical nursing work, oral potassium preparation should be avoided for patients on an empty stomach. Instead, diluting the potassium preparation with warm water and administering it after meals are advised. Additionally, close attention should be paid to the gastrointestinal reaction of patients, and if necessary, it is recommended to use alternative routes of administering potassium.

In terms of nursing outcomes, EFI was positively correlated with mechanical ventilation, days of mechanical ventilation, length of ICU stay, and mortality. Patients on mechanical ventilation have a higher risk of feeding intolerance, possibly due to incomplete sealing of the airway and insufficient cuff pressure during mechanical ventilation, which enable part of the gas to enter the stomach, resulting in a series of gastrointestinal reactions [53]. High balloon pressure can also affect the blood circulation in the airway mucosa. Therefore, for patients receiving mechanical ventilation, it is essential to control the airbag pressure and pay attention to closing the airway, to improve the blood circulation in the airway mucosa and reduce the risk of feeding intolerance. In addition, some studies have suggested that mechanical ventilation can lead to increased intra-abdominal pressure and gastrointestinal dysfunction [54]. According to the study by Mataraso et al., lack of improvement in daily gastric residual volume is an important factor for mortality [6]. Heyland2021 et al. [23] and Plummer et al. [55] found that feeding intolerance was associated with adverse clinical outcomes, such as prolonged mechanical ventilation, prolonged ICU stay, and increased mortality. It was also found that patients with EFI were more likely to undergo malnutrition, and patients with multiple episodes of EFI had a worse prognosis.

Based on the results of this meta-analysis, close attention should be paid to patients with obesity, APACHE II score > 20, renal insufficiency, digestive system diseases, hypoproteinemia, and sepsis, individuals on sedative drugs, vasoactive drugs, and antibiotics, and patients who orally administer potassium agents and undergo mechanical ventilation. In the feeding process, post-pyloric feeding, starting feeding within 48 h, intermittent enteral feeding, nutrition energy up to the standard, and individualized EN implementation plan according to the different conditions of patients could significantly reduce the incidence of EFI, improve adverse outcomes in patients, and shorten the length of ICU stay, and lower mortality.

According to the meta-analysis results of this study, medical workers are reminded to take the following strategies.

First, the following critical patients have a significantly increased risk of EFI and need to be monitored in clinical practice: (i) Patients with metabolic and organ dysfunction, such as obesity, renal insufficiency, and hypoproteinemia;(ii) patients with severe pathological conditions: such as APACHE II score > 20 points, sepsis; (iii) Patients receiving special treatment intervention: such as mechanical ventilation;(iv) Patients using drugs: such as sedatives, vasoactive drugs, use of more than 2 antibiotics, and oral potassium preparation.

Second, based on the evidence-based nutrition support strategy, the following individualized interventions are recommended: (i) In terms of feeding route, post-pyloric feeding is superior; (ii) Early initiation of feeding (within 48 h and within 24 h after stable blood flow) is advisable; (iii) The initial rate of calorie intake was 20–30 mL/h (starting from 15 mL/h in obese or shock patients), and 80% to 100% of the target calorie intake was gradually reached within 72 h. Feeding should be interrupted as much as possible, and continuous feeding and aggressive feeding should be avoided.

Third, dynamic monitoring and adjustment of upper gastrointestinal function is recommended. Gastric residual volume, intra-abdominal pressure and abdominal distension score should be monitored every 4–6 h. Laboratory indexes, such as albumin, lactic acid and inflammatory markers should be monitored daily, and nutritional formula should be adjusted in time.

The prevention and treatment of EFI are critical throughout the whole chain of screening-intervention-monitoring. Medical workers should build a dynamic nutrition management pathway based on individual characteristics of patients and evidence-based strategies such as post-pyloric feeding, early initiation, and gradual target attainment. By optimizing the practice of multidisciplinary collaboration (critical care, nutrition, and pharmacy teams), the incidence of EFI in critically ill patients can eventually be reduced, so as to improve the poor prognosis of critically ill patients.

Strengths and limitations

This study conducts a meta-analysis to systematically integrate multi-dimensional evidence of EFIe in critically ill patients, providing evidence-based guidance for risk prediction and intervention strategies in clinical practice. The core value of this study is to transform fragmented knowledge into actionable conclusions to help realize the precise and individualized management of EN in critically ill patients. This meta-analysis has some limitations. First of all, a total of 23 studies were included in this

analysis, including 12 studies from China and 11 studies from France, the United Kingdom, New Zealand and other countries. Many regional and cultural factors can affect the outcomes of patients. Second, the time points of the studies in the meta-analysis may not be comprehensive. Lastly, another limitation may be a certain degree of partiality in the authors of the included studies. Our meta-analysis results are derived based on the results of these studies, which may cause bias.

Conclusion

The meta-analysis in this study confirmed that EFI was closely associated with the severity of disease, nutritional status, drug use and mechanical ventilation. During the feeding process, post-pyloric feeding, starting feeding within 48 h and reaching the standard of nutritional energy are protective factors for EFI. In the future, it is necessary to standardize the definition of EFI, deepen the mechanism research and carry out precise intervention trials to promote the formulation of future individualized EN support programs.

Abbreviations

BMI Body mass index
EFI Enteral feeding intolerance
EN Enteral nutrition
ORs Odds ratios

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03837-8.

Supplementary Material 1: Search strategy.

Supplementary Material 2: Results of Newcastle-Ottawa Scale scores.

Supplementary Material 3: Results of Agency for Healthcare Research and Quality scores.

Supplementary Material 4: Basic characteristics of the included literature (*n*=23).

Supplementary Material 5: Meta-analysis of influencing factors of enteral nutrition feeding intolerance in critically ill patients.

Acknowledgements

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Writing—original draft preparation: Si Wang, Yang He; Writing—review and editing: Si Wang, Jing Yi; Conceptualization: Si Wang, Yang He; Methodology: Si Wang, Yang He; Formal analysis and investigation: Si Wang, Jing Yi; Funding acquisition: Yang He; Resources: Liyan Sha; Supervision: Si Wang, Liyan Sha, and all authors commented on previous versions of the manuscript. All authors are in agreement with the manuscript and declare that the content has not been published elsewhere.

Funding

This work was supported by the Fundamental Scientific Research Projects of the Educational Department of Liaoning Province [grant number LJKMZ20221268].

Data availability

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 9 January 2025 Accepted: 2 April 2025
Published online: 08 April 2025

References

1. Mehta NM, Skillman HE, Irving SY, Coss-Bu JA, Vermilyea S, Farrington EA, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of critical care medicine and american society for parenteral and enteral nutrition. JPEN J Parenter Enteral Nutr. 2017;41(5):706–42. https://doi.org/10.1177/0148607117711387.
2. Díaz Chavarro BC, Molina-Recio G, Assis Reveiz JK, Romero-Saldaña M. Factors associated with nutritional risk assessment in critically ill patients using the malnutrition universal screening tool (must). J Clin Med. 2024;13(5):1236. https://doi.org/10.3390/jcm13051236.
3. Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, et al. Espen practical and partially revised guideline: Clinical nutrition in the intensive care unit. Clin Nutr. 2023;42(9):1671–89. https://doi.org/10.1016/j.clnu.2023.07.011.
4. 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. https://doi.org/10.1002/ncp.10599.
5. Qiu C, Chen C, Zhang W, Kou Q, Wu S, Zhou L, et al. Fat-modified enteral formula improves feeding tolerance in critically ill patients: A multicenter, single-blind, randomized controlled trial. JPEN J Parenter Enteral Nutr. 2017;41(5):785–95. https://doi.org/10.1177/0148607115601858.
6. Pohlenz-Saw JAE, Merriweather JL, Wandrag L. (mal)nutrition in critical illness and beyond: A narrative review. Anaesthesia. 2023;78(6):770–8. https://doi.org/10.1111/anae.15951.
7. Reintam Blaser A, Malbrain ML, 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. https://doi.org/10.1007/s00134-011-2459-y.
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med. 2009;6(7):e1000100. https://doi.org/10.1371/journal.pmed.1000100.
9. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5. https://doi.org/10.1007/s10654-010-9491-z.
10. Hu J, Dong Y, Chen X, Liu Y, Ma D, Liu X, et al. Prevalence of suicide attempts among Chinese adolescents: A meta-analysis of cross-sectional studies. Compr Psychiatry. 2015;61:78–89. https://doi.org/10.1016/j.comppsych.2015.05.001.
11. Gacouin A, Camus C, Gros A, Isslame S, Marque S, Lavoué S, et al. Constipation in long-term ventilated patients: associated factors and impact on intensive care unit outcomes. Crit Care Med. 2010;38(10):1933–8. https://doi.org/10.1097/CCM.0b013e3181eb9236.
12. Gungabissoon U, Hacquoil K, Bains C, Irizarry M, Dukes G, Williamson R, et al. Prevalence, risk factors, clinical consequences, and treatment of

enteral feed intolerance during critical illness. JPEN J Parenter Enteral Nutr. 2015;39(4):441–8. https://doi.org/10.1177/0148607114526450.
13. Saran D, Brody RA, Stankorb SM, Parrott SJ, Heyland DK. Gastric vs Small Bowel Feeding in Critically Ill Neurologically Injured Patients: Results of a Multicenter Observational Study. JPEN J Parenter Enteral Nutr. 2015;39(8):910–6. https://doi.org/10.1177/0148607114540003.
14. Chen YH: Analysis of the current status and influencing factors of enteral nutrition intolerance in ICU patients in Zhejiang province. Huzhou Normal College: Huzhou Normal College; 2016. https://doi.org/10.7666/d.D01083183.
15. Wang K, McIlroy K, Plank LD, Petrov MS, Windsor JA. Prevalence, Outcomes, and Management of Enteral Tube Feeding Intolerance: A Retrospective Cohort Study in a Tertiary Center. JPEN J Parenter Enteral Nutr. 2017;41(6):959–67. https://doi.org/10.1177/0148607115627142.
16. Zhou TT, Wang BR, Zhu XF, Qiao Y, Wang YT, Qiao Y, et al. Factors Related to Enteral Feeding Intolerance of Septic Patients in ICU. J Nurs. 2017;24(16):6–9.
17. Atasever AG, Ozcan PE, Kasali K, Abdullah T, Orhun G, Senturk E. The frequency, risk factors, and complications of gastrointestinal dysfunction during enteral nutrition in critically ill patients. Ther Clin Risk Manag. 2018;14:385–91. https://doi.org/10.2147/tcrm.S158492.
18. Ren S, He C, Li YQ, Shen LM, Zhao HL. Analysis of factors influencing enteral nutrition intolerance in patients with sepsis. Parenteral Enteral Nutr. 2018;25(06):355–8. https://doi.org/10.16151/j.1007-810x.2018.11.008.
19. Chen W, Wang H, Chen Y, Yuan D, Chen R. The independent risk factors of early diarrhoea in enteral nutrition for ICU patients. J Int Med Res. 2019;47(10):4929–39. https://doi.org/10.1177/0300060519868340.
20. McNelly AS, Bear DE, Connolly BA, Arbane G, Allum L, Tarbhai A, et al. Effect of Intermittent or Continuous Feed on Muscle Wasting in Critical Illness: A Phase 2 Clinical Trial. Chest. 2020;158(1):183–94. https://doi.org/10.1016/j.chest.2020.03.045.
21. Sabino KM, Fuller J, May S, Wakefield D. Safety and Tolerance of Enteral Nutrition in the Medical and Surgical Intensive Care Unit Patient Receiving Vasopressors. Nutr Clin Pract. 2021;36(1):192–200. https://doi.org/10.1002/ncp.10548.
22. Chen L, Chen YF, Yu AH, Yin F. Status quo of feeding intolerance of critically ill patients with enteral nutrition in neurology department and its influencing factors. Chin Nurs Res. 2021;35(07):1285–9.
23. Heyland DK, Ortiz A, Stoppe C, Patel JJ, Yeh DD, Dukes G, et al. Incidence, Risk Factors, and Clinical Consequence of Enteral Feeding Intolerance in the Mechanically Ventilated Critically Ill: An Analysis of a Multicenter. Multiyear Database Crit Care Med. 2021;49(1):49–59. https://doi.org/10.1097/ccm.0000000000004712.
24. Yahyapoor F, Dehnavi Z, Askari G, Ranjbar G, Hejri Zarifi S, Bagherniya M, et al. The prevalence and possible causes of enteral tube feeding intolerance in critically ill patients: A cross-sectional study. J Res Med Sci. 2021;26:60. https://doi.org/10.4103/jrms.JRMS_689_20.
25. Geng ZJ, Yin WC, Jiao HB, Zhao YX. Enteral nutritional feeding intolerance in ICU patients with clinical medi-cal conditions and its influencing factors. China Modern Doctor. 2022;60(4):105-7,11.
26. Hong-Yeul L. Continuous versus Intermittent Enteral Tube Feeding for Critically Ill Patients: A Prospective, Randomized Controlled Trial. Nutrients. 2022;14(3):664.
27. Arunachala Murthy T, Chapple LS, Lange K, Marathe CS, Horowitz M, Peake SL, et al. Gastrointestinal dysfunction during enteral nutrition delivery in intensive care unit (ICU) patients: Risk factors, natural history, and clinical implications. A post-hoc analysis of The Augmented versus Routine approach to Giving Energy Trial (TARGET). Am J Clin Nutr. 2022;116(2):589–98. https://doi.org/10.1093/ajcn/nqac113.
28. Ni R, Chen YY, Zuo L, Sun MM, Sun Y. Study on the current status of intolerance to enteral nutrition feeding in critically ill patients and the factors affecting it. South China J Prev Med. 2022;48(09):1140–2.
29. Kunrong Y, Na G, Dingding Z, Ying X, Yanling M, Li W, et al. Prevalence and risk factors of enteral nutrition intolerance in intensive care unit patients: a retrospective study. Chin Med J. 2022;135(15):1814–20.
30. Zhang J, Zhang YY, You HQ. Influencing factors of enteral nutrition?related diarrhea in elderly patients in intensive care unit. Chin Nurs Res. 2022;36(14):2624–6.
31. Zhu J, Li HY, Gong YL. Comparison of the effects of intermittent versus continuous enteral nutrition on feeding intolerance in ICU patients with cerebral haemorrhage. Modern J Integr Trad Chin Western Med. 2022;31(23):3347–50+58.
32. Zhang LH, Zhang L, Zhang LP, Wu Y, Xi M. Enteral nutrition feeding intolerance and its influencing factors in patients with sepsis. South China J Prev Med. 2023;49(02):174–8.
33. Hu HY, Jiang LY, Hu HZ, Fei KH. Influence of different gastric residual volume on the feeding compliance rate of enteral nutrition patients in ICU and analysis of risk factors. J Nurs Train. 2024;7:711–5.
34. Nguyen VTT. Aging of enteric neuromuscular systems in gastrointestinal tract. Neurogastroenterol Motil. 2022;34(6):e14352.
35. Zhang W, Jiang HJ, Jiang XG, Li K, Wu YD, Zhang LY. Meta-analysis of risk factors for intolerance to enteral nutritional feeding in critically ill patients. Parent Enteral Nutr. 2020;27(5):313–20
36. Nehra V, Allen JM, Mailing LJ, Kashyap PC, Woods JA. Gut Microbiota: Modulation of Host Physiology in Obesity. Physiology (Bethesda). 2016;31(5):327–35. https://doi.org/10.1152/physiol.00005.2016.
37. Zhong J, Kirabo A, Yang HC, Fogo AB, Shelton EL, Kon V. Intestinal Lymphatic Dysfunction in Kidney Disease. Circ Res. 2023;132(9):1226–45. https://doi.org/10.1161/circresaha.122.321671.
38. Reintam Blaser A, Bachmann KF, Deane AM. Gastrointestinal function in critically ill patients. Curr Opin Clin Nutr Metab Care. 2023;26(5):463–9. https://doi.org/10.1097/mco.0000000000000955.
39. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2013;108(1):18–37. https://doi.org/10.1038/ajg.2012.373. quiz 8.
40. Acosta-Escribano J, Fernández-Vivas M, Grau Carmona T, Caturla-Such J, Garcia-Martinez M, Menendez-Mainer A, et al. Gastric versus transpyloric feeding in severe traumatic brain injury: a prospective, randomized trial. Intensive Care Med. 2010;36(9):1532–9. https://doi.org/10.1007/s00134-010-1908-3.
41. Zhang Z. Comparison of postpyloric tube feeding and gastric tube feeding in intensive care unit patients: A meta-analysis. Nutr Clin Pract. 2013;28(3):371–80.
42. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017;43(3):380–98. https://doi.org/10.1007/s00134-016-4665-0.
43. Bakker OJ, van Brunschot S, Farre A, Johnson CD, Kalfarentzos F, Louie BE, et al. Timing of enteral nutrition in acute pancreatitis: meta-analysis of individuals using a single-arm of randomised trials. Pancreatology. 2014;14(5):340–6. https://doi.org/10.1016/j.pan.2014.07.008.
44. 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. https://doi.org/10.1016/j.clnu.2018.08.037.
45. Eveleens RD, Joosten KFM, de Koning BAE, Hulst JM, Verbruggen S. Definitions, predictors and outcomes of feeding intolerance in critically ill children: A systematic review. Clin Nutr. 2020;39(3):685–93. https://doi.org/10.1016/j.clnu.2019.03.026.
46. Shi YM, Bai L, Zhou YT, Zhang SX. Research progress on influencing factors of diarrhea in patients during enteral nutrition. Chin Nurs Res. 2017;31(14):1673–6.
47. Oami T, Chihade DB, Coopersmith CM. The microbiome and nutrition in critical illness. Curr Opin Crit Care. 2019;25(2):145–9. https://doi.org/10.1097/mcc.0000000000000582.
48. He P. Study on the efficacy of added probiotic therapy on early gastrointestinal dyskinesia in patients with severe ischaemic stroke. Suzhou University: Suzhou University; 2017.
49. Wang W, Yue Y, Hao LL, Yao P, Wei JJ. Clinical effect of probiotics on treatment of antibiotic-associated diarrhea. Chin J Nosocomiol. 2016;26(06):1258–60.
50. Malik AA, Rajandram R, Tah PC, Hakumat-Rai VR, Chin KF. Microbial cell preparation in enteral feeding in critically ill patients: A randomized, double-blind, placebo-controlled clinical trial. J Crit Care. 2016;32:182–8. https://doi.org/10.1016/j.jcrc.2015.12.008.
51. Wei J, Lin FY, Mo HP, Feng YY. A retrospective analysis of factors related to diarrhea during enteral nutrition in ICU patients. Chin J Nurs. 2015;50(08):954–9.
52. Chen T, Wang T, Li Q, He Y, Chen LL, Zhu JC. Current status and influencing factors of enteral feeding intolerance in patients with severe acute pancreatitis. Chin J Nurs. 2017;52(06):716–20.

53. Hou F, Gao J, Zhao RL, Su L, Zhang L. Study on relationship between enteral nutrition feeding intolerance and ICU acquired weakness in mechanical ventilation patients with chronic obstructive pulmonary disease during acute exacerbation. J Clin Pulmon Med. 2022;27(1):36–40.
54. Rafiei MR, Aghadavoudi O, Shekarchi B, Sajjadi SS, Masoudifar M. Can selection of mechanical ventilation mode prevent increased intra-abdominal pressure in patients admitted to the intensive care unit? Int J Prev Med. 2013;4(5):552–6.
55. Plummer MP, Reintam Blaser A, Deane AM. Gut dysmotility in the ICU: diagnosis and therapeutic options. Curr Opin Crit Care. 2019;25(2):138–44. https://doi.org/10.1097/mcc.0000000000000581.

Publisher's Note