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

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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

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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



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[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 \geq 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 \geq 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 guality 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 I² 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 randomeffects 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, I²=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, I²=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

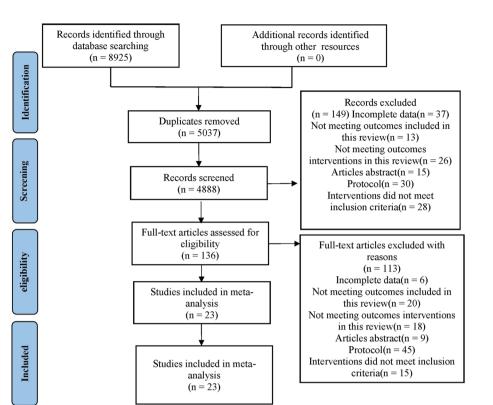


Fig. 1 Flow chart of literature screening

	Exp	eriment	al		Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Atasever 2018	62	18	86	60	20	51	3.9%	2.00 [-4.68, 8.68]	
Chen2019	67	20.7	164	65	20	369	8.2%	2.00 [-1.77, 5.77]	
Gacouin2010	61	17.8	353	60.3	15.6	256	10.9%	0.70 [-1.96, 3.36]	_ _
Gungabissoon2015	56.7	17.97	576	57.9	17.46	1312	13.6%	-1.20 [-2.95, 0.55]	
Heyland2021	58.1	17.7	4036	59.8	17.6	11882	16.1%	-1.70 [-2.33, -1.07]	+
Hu2024	56.1	10.3	57	57.3	9.9	461	10.5%	-1.20 [-4.02, 1.62]	
Murthy 2022	56	16.8	1777	58.5	16.1	2099	15.4%	-2.50 [-3.54, -1.46]	+
Ren2018	70.36	12.33	89	61.73	16.09	101	7.6%	8.63 [4.58, 12.68]	
Yahyapoor2021	56.9	18.41	162	61.3	20.49	83	5.5%	-4.40 [-9.64, 0.84]	
Yu 2022	50	19	114	57	19	863	8.3%	-7.00 [-10.71, -3.29]	
Total (95% CI)			7414			17477	100.0%	-0.80 [-2.31, 0.71]	•
Heterogeneity: Tau ² =	= 3.57; 0	$Chi^2 = 4$	4.45, d	f = 9 (P)	< 0.00	001); I ² =	= 80%		
Test for overall effect	,					., -			–20 –10 Ó 10 20 Favours [experimental] Favours [control]

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

	Exp	eriment	al		Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Atasever 2018	62	18	86	60	20	51	2.4%	2.00 [-4.68, 8.68]	
Chen2019	67	20.7	164	65	20	369	6.4%	2.00 [-1.77, 5.77]	
Gacouin2010	61	17.8	353	60.3	15.6	256	10.3%	0.70 [-1.96, 3.36]	
Gungabissoon2015	56.7	17.97	576	57.9	17.46	1312	15.7%	-1.20 [-2.95, 0.55]	
Heyland2021	58.1	17.7	4036	59.8	17.6	11882	24.1%	-1.70 [-2.33, -1.07]	• •
Hu2024	56.1	10.3	57	57.3	9.9	461	9.6%	-1.20 [-4.02, 1.62]	
Murthy 2022	56	16.8	1777	58.5	16.1	2099	21.2%	-2.50 [-3.54, -1.46]	+
Ren2018	70.36	12.33	89	61.73	16.09	101	0.0%	8.63 [4.58, 12.68]	
Yahyapoor2021	56.9	18.41	162	61.3	20.49	83	3.7%	-4.40 [-9.64, 0.84]	
Yu 2022	50	19	114	57	19	863	6.5%	-7.00 [-10.71, -3.29]	
Total (95% CI)			7325			17376	100.0%	-1.62 [-2.71, -0.52]	•
Heterogeneity: Tau ² =	= 1.19; C	$chi^2 = 1$	9.47, d	f = 8 (P					
Test for overall effect	: Z = 2.8	89 (P = 0	0.004)			–20 –10 Ó 10 20 Favours [experimental] Favours [control]			

Fig. 3 The relationship between age and EFI

	Expe	erimer	tal	c	ontrol		5	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Atasever 2018	27	4.7	86	27	6.4	51	4.2%	0.00 [-0.35, 0.35]	
Chen2019	22	3.1	162	21.6	3.4	369	11.5%	0.12 [-0.06, 0.31]	—
Gungabissoon2015	27.9	8.31	576	27.9	8.11	1312	22.4%	0.00 [-0.10, 0.10]	-
Heyland2021	27.6	7.6	4036	27.3	7.8	11882	33.2%	0.04 [0.00, 0.07]	-
Murthy 2022	28.9	7.5	1777	29.6	8	2099	28.7%	-0.09 [-0.15, -0.03]	-
Total (95% CI)			6637				100.0%	0.00 [-0.08, 0.08]	• • • •
Heterogeneity: Tau ² = Test for overall effect					-1 -0.5 0 0.5 1 Favours [experimental] Favours [control]				

Fig. 4 The relationship between BMI and EFI

	Expe	erimer	ntal	c	Contro	I I	1	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Atasever 2018	27	4.7	86	27	6.4	51	0.9%	0.00 [-0.35, 0.35]	
Chen2019	22	3.1	162	21.6	3.4	369	3.2%	0.12 [-0.06, 0.31]	+
Gungabissoon2015	27.9	8.31	576	27.9	8.11	1312	11.3%	0.00 [-0.10, 0.10]	-+-
Heyland2021	27.6	7.6	4036	27.3	7.8	11882	84.7%	0.04 [0.00, 0.07]	
Murthy 2022	28.9	7.5	1777	29.6	8	2099	0.0%	-0.09 [-0.15, -0.03]	
Total (95% CI)			4860			13614	100.0%	0.04 [0.00, 0.07]	*
Heterogeneity: Chi ² = Test for overall effect					-1 -0.5 0 0.5 1 Favours [experimental] Favours [control]				

Fig. 5 The relationship between BMI and EFI

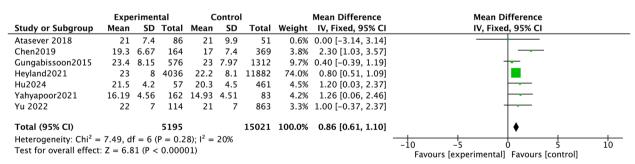


Fig. 6 The relationship between APACHE II score and EFI

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, I²=43%), and the

	Experim	ental	Conti	rol		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Atasever 2018	16	86	9	51	24.2%	1.07 [0.43, 2.63]	_	
Hu2024	15	57	45	461	33.2%	3.30 [1.70, 6.42]		
Yu 2022	27	114	136	863	42.7%	1.66 [1.04, 2.65]		
Total (95% CI)		257		1375	100.0%	1.87 [1.05, 3.33]	•	
Total events	58		190					
Heterogeneity: Tau ² = Test for overall effect				(P = 0	.10); $I^2 = 5$	56%	0.01 0.1 1 10 10 Favours [experimental] Favours [control]	Τę

Fig. 7 The relationship between renal insufficiency and EFI

	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Chen2019	2	164	7	369	0.6%	0.64 [0.13, 3.06]	
Gungabissoon2015	34	576	57	1312	5.2%	1.36 [0.90, 2.05]	
Heyland2021	506	4036	1097	11882	83.9%	1.36 [1.23, 1.50]	
Murthy 2022	78	1777	60	2099	8.3%	1.54 [1.10, 2.14]	
Ren2018	10	89	10	101	1.4%	1.13 [0.50, 2.60]	
Wang2017	2	162	5	293	0.5%	0.72 [0.14, 3.69]	
Total (95% CI)		6804		16056	100.0%	1.36 [1.24, 1.49]	•
Total events	632		1236				
Heterogeneity: Chi ² =	2.16, df	= 5 (P =	0.83); I ²	= 0%			0.01 0.1 1 10 100
Test for overall effect	Z = 6.60	(P < 0.0	00001)				Favours [experimental] Favours [control]

Fig. 8 The relationship between digestive system diseases and EFI

	Expe	Experimental Control						Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Chen2019	32.4	5.78	164	32.5	6.75	369	11.4%	-0.10 [-1.22, 1.02]	
Murthy 2022	28.1	6.5	1777	28.8	6.2	2099	88.6%	-0.70 [-1.10, -0.30]	-#-
Total (95% CI)			1941			2468	100.0%	-0.63 [-1.01, -0.25]	◆
Heterogeneity: Chi ² =	0.97, d	f = 1 (P = 0.3	32); I ² =	0%				
Test for overall effect	: Z = 3.2	27 (P =	0.001)					Favours [experimental] Favours [control]

Fig. 9 The relationship between hypoproteinemia and EFI

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Chen2019	8	164	10	369	0.7%	1.84 [0.71, 4.75]	
Gungabissoon2015	75	576	134	1312	8.8%	1.32 [0.97, 1.78]	
Heyland2021	489	4036	1181	11882	64.9%	1.25 [1.12, 1.40]	
Hu2024	14	57	99	461	2.0%	1.19 [0.63, 2.26]	
Murthy 2022	170	1777	186	2099	19.0%	1.09 [0.87, 1.35]	- - -
Yahyapoor2021	45	162	10	83	1.2%	2.81 [1.33, 5.91]	
Yu 2022	25	114	150	863	3.4%	1.34 [0.83, 2.15]	—
Total (95% CI)		6886		17069	100.0%	1.25 [1.14, 1.37]	•
Total events	826		1770				
Heterogeneity: Chi ² =	= 6.93, df =	= 6 (P =	0.33); I ²	= 13%			0.05 0.2 1 5 20
Test for overall effect	t: Z = 4.80	(P < 0.	00001)				Favours [experimental] Favours [control]

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

Experim					Odds Ratio	Odds Ratio
Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% Cl
33	119	64	148	13.7%	0.50 [0.30, 0.84]	
26	164	75	369	14.0%	0.74 [0.45, 1.21]	
30	1777	111	2099	14.8%	0.31 [0.20, 0.46]	
22	89	53	101	12.6%	0.30 [0.16, 0.55]	_ _
4	280	84	1215	8.8%	0.20 [0.07, 0.54]	
20	162	40	293	13.1%	0.89 [0.50, 1.58]	
82	218	113	308	15.3%	1.04 [0.73, 1.49]	+
6	46	7	60	7.6%	1.14 [0.35, 3.64]	
	2855		4593	100.0%	0.54 [0.35, 0.84]	•
223		547				
0.29; Chi	$i^2 = 33.$	34, df =	0.01 0.1 1 10 100			
Z = 2.75	(P = 0.0)	006)				Favours [experimental] Favours [control]
•	Events 33 26 30 22 4 20 82 6 223 0.29; Chi	33 119 26 164 30 1777 22 89 4 280 20 162 82 218 6 46 2855 223 0.29; Chi ² = 33.	Total Events 33 119 64 26 164 75 30 1777 111 22 89 53 4 280 84 20 162 40 82 218 113 6 46 7 2855 223 547	TotalEventsTotal3311964148261647536930177711120992289531014280841215201624029382218113308646760285545932235470.29; Chi² = 33.34, df = 7 (P < 100)	TotalEventsTotalWeight331196414813.7%261647536914.0%301777111209914.8%22895310112.6%42808412158.8%201624029313.1%8221811330815.3%6467607.6%285545932035470.29; Chi ² = 33.34, df = 7 (P < 0.0001);	EventsTotalEventsTotalWeightM-H, Random, 95% CI331196414813.7%0.50[0.30, 0.84]261647536914.0%0.74[0.45, 1.21]301777111209914.8%0.31[0.20, 0.46]22895310112.6%0.30[0.16, 0.55]42808412158.8%0.20[0.07, 0.54]201624029313.1%0.89[0.50, 1.58]8221811330815.3%1.04[0.73, 1.49]6467607.6%1.14[0.35, 3.64]28554593100.0%0.54[0.35, 0.84]2235470.29; Chi ² = 33.34, df = 7 (P < 0.0001); l ² = 79%10.0%10.0001

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

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Chen2016	33	119	64	148	16.5%	0.50 [0.30, 0.84]	
Chen2019	26	164	75	369	17.0%	0.74 [0.45, 1.21]	
Murthy 2022	30	1777	111	2099	18.3%	0.31 [0.20, 0.46]	
Ren2018	22	89	53	101	14.9%	0.30 [0.16, 0.55]	_ -
Saran2015	4	280	84	1215	9.6%	0.20 [0.07, 0.54]	
Wang2017	20	162	40	293	15.6%	0.89 [0.50, 1.58]	— —
Zhang2023	82	218	113	308	0.0%	1.04 [0.73, 1.49]	
Zhou2017	6	46	7	60	8.1%	1.14 [0.35, 3.64]	
Total (95% CI)		2637		4285	100.0%	0.48 [0.32, 0.74]	•
Total events	141		434				
Heterogeneity: Tau ² =	= 0.21; Ch	$i^2 = 19.$	62, df =	6 (P =	0.003); I ²	= 69%	0.01 0.1 1 10 100
Test for overall effect	: Z = 3.40	(P = 0.)	0007)				0.01 0.1 1 10 100 Favours [experimental] Favours [control]

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

Odds Ratio Experimental Control Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% CI Chen2016 0.54 [0.30, 0.95] 83 119 120 148 16.7% Chen2019 138 164 319 369 16.9% 0.83 [0.50, 1.39] Geng2022 196 352 17.4% 0.37 [0.28, 0.50] 410 532 Ren2018 46 89 101 16.7% 1.14 [0.64, 2.01] 49 Zhang2022 74 127 19 173 16.6% 11.32 [6.26, 20.47] 26 Zhou2017 46 47 60 15.7% 0.36 [0.15, 0.84] Total (95% CI) 897 1383 100.0% 0.96 [0.36, 2.58] Total events 563 964 Heterogeneity: Tau² = 1.44; Chi² = 109.72, df = 5 (P < 0.00001); $I^2 = 95\%$ 0.01 100 0.1 10 Test for overall effect: Z = 0.08 (P = 0.93)Favours [experimental] Favours [control]

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, I²=47%), and the metaanalysis 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.

Study or Subgroup

Subtotal (95% CI)

13.2.2 Surgical group

Chen2016

Geng2022

Zhou2017

Total events

Chen2019

Zhang2022

Total events

Total (95% CI)

Total events

Subtotal (95% CI)

Ren2018

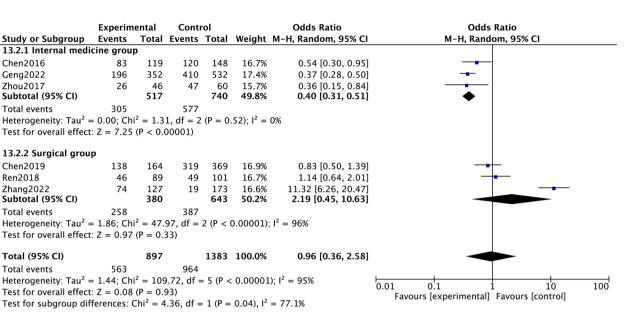


Fig. 14 The relationship between the starting EN within 48 h and EFI

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chen2019	139	164	296	369	47.0%	1.37 [0.83, 2.25]	+=-
Lee2022	22	44	27	56	20.1%	1.07 [0.49, 2.37]	_
Murthy 2022	18	41	41	80	26.4%	0.74 [0.35, 1.59]	
Zhu2022	15	21	28	65	6.6%	3.30 [1.14, 9.60]	
Total (95% CI)		270		570	100.0%	1.27 [0.90, 1.79]	◆
Total events	194		392				
Heterogeneity: Chi ² =	5.27, df =	= 3 (P =	0.15); I ²	= 43%			0.05 0.2 1 5 20
Test for overall effect	: Z = 1.39	(P = 0.	17)				Favours [experimental] Favours [control]

Fig. 15 The relationship between EN patterns and EFI

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Chen2019	139	164	296	369	63.8%	1.37 [0.83, 2.25]	+=-
Lee2022	22	44	27	56	27.3%	1.07 [0.49, 2.37]	_
Murthy 2022	18	41	41	80	0.0%	0.74 [0.35, 1.59]	
Zhu2022	15	21	28	65	9.0%	3.30 [1.14, 9.60]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		229		490	100.0%	1.46 [0.99, 2.16]	◆
Total events	176		351				
Heterogeneity: Chi ² =	= 2.89, df =	= 2 (P =	0.24); I ²	= 31%			0.05 0.2 1 5 20
Test for overall effect	:: Z = 1.92	(P= 0 .	05)				Favours [experimental] Favours [control]

Fig. 16 The relationship between EN patterns and EFI

	Expe	erimer	ntal	C	ontro	I		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Gungabissoon2015	55.6	23	576	64.3	23.6	1312	16.0%	-8.70 [-10.97, -6.43]	
Heyland2021	51.1	27.3	4036	58.1	29.2	11882	84.0%	-7.00 [-7.99, -6.01]	.
Total (95% CI)			4612			13194	100.0%	-7.27 [-8.18, -6.36]	◆
Heterogeneity: Chi ² = Test for overall effect					45%				-10 -5 0 5 10 Favours [experimental] Favours [control]

Fig. 17 The relationship between nutritional formula and EFI

	Experim	iental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Atasever 2018	57	86	37	51	6.7%	0.74 [0.35, 1.59]	.
Geng2022	142	352	150	532	30.5%	1.72 [1.30, 2.29]	
Hu2024	37	57	188	461	6.2%	2.69 [1.51, 4.77]	
Ren2018	45	89	46	101	9.1%	1.22 [0.69, 2.16]	- -
Yu 2022	72	114	420	863	15.5%	1.81 [1.21, 2.71]	
Zhang2022	54	127	67	173	14.0%	1.17 [0.73, 1.87]	_ _
Zhang2023	161	218	171	308	15.9%	2.26 [1.55, 3.30]	
Zhou2017	41	46	52	60	2.1%	1.26 [0.38, 4.15]	
Total (95% CI)		1089		2549	100.0%	1.68 [1.44, 1.97]	•
Total events	609		1131				
Heterogeneity: Chi ² =	= 13.26, df	f = 7 (P	= 0.07);	$l^2 = 47$	%		
Test for overall effect	z = 6.40	(P < 0.	00001)				0.01 0.1 1 10 100 Favours [experimental] Favours [control]

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

	Experim	ental	Conti	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Atasever 2018	50	86	21	51	9.5%	1.98 [0.98, 4.01]	
Chen2019	67	164	110	369	14.6%	1.63 [1.11, 2.39]	
Geng2022	98	352	64	532	15.2%	2.82 [1.99, 4.00]	
Murthy 2022	1559	1777	1599	2099	17.9%	2.24 [1.88, 2.66]	-
Ren2018	52	89	50	101	11.4%	1.43 [0.81, 2.55]	
Sabino2021	32	40	146	279	8.1%	3.64 [1.62, 8.19]	
Zhang2023	82	218	123	308	15.1%	0.91 [0.63, 1.30]	
Zhou2017	31	46	29	60	8.3%	2.21 [0.99, 4.91]	
Total (95% CI)		2772		3799	100.0%	1.89 [1.39, 2.56]	•
Total events	1971		2142				
Heterogeneity: Tau ² =	= 0.13; Ch	$i^2 = 28.$	72, df =	7 (P =	0.0002);	$^{2} = 76\%$	
Test for overall effect	:: Z = 4.06	(P < 0.	0001)				0.01 0.1 i 10 100 Favours [experimental] Favours [control]

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

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Atasever 2018	50	86	21	51	3.6%	1.98 [0.98, 4.01]	
Chen2019	67	164	110	369	13.2%	1.63 [1.11, 2.39]	
Geng2022	98	352	64	532	12.1%	2.82 [1.99, 4.00]	
Murthy 2022	1559	1777	1599	2099	59.4%	2.24 [1.88, 2.66]	
Ren2018	52	89	50	101	6.4%	1.43 [0.81, 2.55]	
Sabino2021	32	40	146	279	2.4%	3.64 [1.62, 8.19]	
Zhang2023	82	218	123	308	0.0%	0.91 [0.63, 1.30]	
Zhou2017	31	46	29	60	2.7%	2.21 [0.99, 4.91]	
Total (95% CI)		2554		3491	100.0%	2.20 [1.93, 2.51]	•
Total events	1889		2019				
Heterogeneity: Chi ² =	8.08, df	= 6 (P =	0.23); I ²	= 26%			
Test for overall effect	: Z = 11.6	3 (P < 0	.00001)				0.01 0.1 1 10 100 Favours [experimental] Favours [control]

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.

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Chen2021	39	69	25	74	5.6%	2.55 [1.29, 5.02]	
Geng2022	256	352	286	532	33.1%	2.29 [1.72, 3.07]	
Ni2022	187	314	194	486	32.9%	2.22 [1.66, 2.96]	
Zhang2023	126	218	140	308	26.1%	1.64 [1.16, 2.33]	
Zhou2017	38	46	28	60	2.3%	5.43 [2.17, 13.56]	
Total (95% CI)		999		1460	100.0%	2.18 [1.85, 2.58]	•
Total events	646		673				
Heterogeneity: Chi ² =	= 6.65, df =	= 4 (P =	0.16); I ²	$^{2} = 40\%$			
Test for overall effect	:: Z = 9.14	(P < 0.	00001)				0.05 0.2 İ 5 20 Favours [experimental] Favours [control]

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

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Geng2022	210	352	154	532	37.3%	3.63 [2.73, 4.82]	-
Zhang2023	112	218	119	308	36.6%	1.68 [1.18, 2.38]	
Zhou2017	39	46	13	60	26.1%	20.14 [7.32, 55.42]	
Total (95% CI)		616		900	100.0%	4.28 [1.73, 10.59]	
Total events	361		286				
Heterogeneity: Tau ² = Test for overall effect	,		,	2 (P <	0.00001)	$; I^2 = 92\%$	0.01 0.1 1 10 100 Favours [experimental] Favours [control]

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

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
Chen2019	67	164	110	369	13.7%	1.63 [1.11, 2.39]	
Chen2021	45	69	30	74	3.4%	2.75 [1.39, 5.42]	
Geng2022	242	352	272	532	23.2%	2.10 [1.59, 2.79]	
Hu2024	48	57	290	461	3.4%	3.14 [1.51, 6.57]	
Ni2022	109	314	98	486	17.2%	2.11 [1.53, 2.90]	-
Ren2018	42	89	46	101	7.8%	1.07 [0.60, 1.89]	
Yu 2022	97	114	623	863	7.4%	2.20 [1.29, 3.76]	
Zhang2022	92	127	100	173	8.0%	1.92 [1.17, 3.14]	
Zhang2023	151	218	159	308	13.9%	2.11 [1.47, 3.04]	
Zhou2017	40	46	53	60	2.1%	0.88 [0.27, 2.82]	
Total (95% CI)		1550		3427	100.0%	1.98 [1.73, 2.28]	•
Total events	933		1781				
Heterogeneity: Chi ² =	10.36, df	^F = 9 (P	= 0.32);	$I^2 = 13$	%		0.01 0.1 1 10 100
Test for overall effect	: Z = 9.73	(P < 0.	00001)				0.01 0.1 1 10 100 Favours [experimental] Favours [control]

Fig. 23 The relationship between mechanical ventilation and EFI

	Expe	erimen	tal	C	ontrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Chen2019	6.3	5.16	164	5	4.44	369	36.0%	1.30 [0.39, 2.21]] 🗕	
Gacouin2010	15.7	11.1	353	12	6.9	256	34.7%	3.70 [2.27, 5.13]] 🗖	
Yahyapoor2021	13.48	16.9	162	4.58	5.16	83	29.3%	8.90 [6.07, 11.73]	•	
Total (95% CI)			679				100.0%		, , ♦	
Heterogeneity: Tau ² = Test for overall effect				df = 2	(P < 0	.00001)); I ² = 939	6	-100 -50 0 50 Favours [experimental] Favours [control]	100

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

	Exp	eriment	al	c	ontro	I		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Atasever 2018	21.4	17	86	16	18.5	51	5.5%	5.40 [-0.82, 11.62]	
Chen2019	12.3	7.41	164	9.3	5.19	369	17.3%	3.00 [1.75, 4.25]	•
Gacouin2010	19.7	13.3	353	16.7	9.6	256	15.7%	3.00 [1.18, 4.82]	=
Gungabissoon2015	15.8	11.04	576	13	9.33	1312	17.8%	2.80 [1.77, 3.83]	•
Heyland2021	16.23	12.2	4036	12.03	9.5	11882	18.8%	4.20 [3.79, 4.61]	•
Hu2024	14.3	3.2	57	14.7	4	461	18.0%	-0.40 [-1.31, 0.51]	•
Yahyapoor2021	17.38	17.5	162	15.57	21.1	83	6.9%	1.81 [-3.47, 7.09]	+-
Total (95% CI)			5434			14414	100.0%	2.63 [0.89, 4.37]	•
Heterogeneity: Tau ² =	= 4.16; 0	$chi^2 = 8$	4.05, d	f = 6 (P)	< 0.0	0001); I ²	= 93%		
Test for overall effect	z = 2.9	96 (P =	0.003)						Favours [experimental] Favours [control]

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

	Exp	eriment	tal	c	Contro	I		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Atasever 2018	21.4	17	86	16	18.5	51	1.6%	5.40 [-0.82, 11.62]	
Chen2019	12.3	7.41	164	9.3	5.19	369	20.8%	3.00 [1.75, 4.25]	•
Gacouin2010	19.7	13.3	353	16.7	9.6	256	13.4%	3.00 [1.18, 4.82]	-
Gungabissoon2015	15.8	11.04	576	13	9.33	1312	24.7%	2.80 [1.77, 3.83]	•
Heyland2021	16.23	12.2	4036	12.03	9.5	11882	37.3%	4.20 [3.79, 4.61]	
Hu2024	14.3	3.2	57	14.7	4	461	0.0%	-0.40 [-1.31, 0.51]	
Yahyapoor2021	17.38	17.5	162	15.57	21.1	83	2.2%	1.81 [-3.47, 7.09]	÷-
Total (95% CI)			5377			13953	100.0%	3.41 [2.60, 4.22]	•
Heterogeneity: Tau ² =	= 0.41; 0	$Chi^2 = 1$	0.12, d	lf = 5 (P	= 0.0	7); $I^2 = 5$	51%		-100 -50 0 50 100
Test for overall effect	t: Z = 8.2	25 (P <	0.0000	1)					-100 -50 0 50 100 Favours [experimental] Favours [control]

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

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Atasever 2018	43	86	18	51	0.8%	1.83 [0.90, 3.74]	
Chen2019	38	164	54	369	1.7%	1.76 [1.11, 2.80]	
Gungabissoon2015	177	576	344	1312	9.7%	1.25 [1.01, 1.55]	
Heyland2021	1251	4036	2798	11882	65.6%	1.46 [1.35, 1.58]	
Murthy 2022	517	1777	484	2099	21.1%	1.37 [1.19, 1.58]	-
Wang2017	32	162	29	293	1.1%	2.24 [1.30, 3.86]	
Total (95% CI)		6801		16006	100.0%	1.44 [1.35, 1.53]	•
Total events	2058		3727				
Heterogeneity: Chi ² =	= 5.94, df =	= 5 (P =	0.31); I ²	= 16%		-	0,1 0,2 0,5 1 2 5 10
Test for overall effect	:: Z = 10.9	8 (P < 0	.00001)				0.1 0.2 0.5 1 2 5 10 Favours [experimental] Favours [control]

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

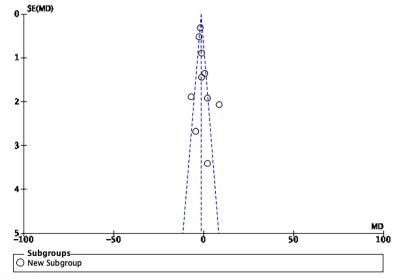


Fig. 28 Funnel plot of publication bias

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, postpyloric 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-interventionmonitoring. 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

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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.

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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.

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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.

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