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Safety and efficacy of enteral nutrition during prone ventilation: A meta-analysis

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Abstract

Background: Prone ventilation improves lung function in patients with acute respiratory distress syndrome by enhancing oxygenation; however, managing enteral nutrition during prone ventilation is challenging due to body position changes.

Objective: The objective of the study was to assess the safety and efficacy of enteral nutrition during prone ventilation. A meta-analysis was conducted to evaluate the efficacy and safety of enteral nutrition in the prone position in critically ill ventilated patients.

Methods: By searching databases such as PubMed, Embase, Cochrane Library, Web of Science, Cumulative Index of Nursing and Allied Health Literature, and WanFang Data, the relevant literature was retrieved from their inception to 24 December 2024. The Newcastle–Ottawa Scale was used to evaluate article quality. Egger's test was used to check for publication bias, and Review Manager 5.4 was used to conduct the analyses.

Results: Among 81 publications, five studies with a total sample size of 319 were included in this study. Enteral nutrition in the prone position, compared with that in the supine position, was associated with a lower energy achievement rate (mean difference: −0.88; 95% confidence interval: −1.83 to 0.06; $P < 0.00001$), no significant difference in mortality (odds ratio: 1.11; 95% confidence interval: 0.65 to 1.88; $P = 0.7$), a greater incidence of ventilator-associated pneumonia (odds ratio: 2.11; 95% confidence interval: 1.12 to 3.96; $P = 0.02$), more frequent vomiting (odds ratio: 2.38; 95% confidence interval: 1.61 to 3.50; $P < 0.0001$), a greater gastric residual volume (odds ratio: 2.72; 95% confidence interval: 1.47 to 5.03; $P = 0.001$), and increased interruptions in enteral nutrition (odds ratio: 4.75; 95% confidence interval: 2.22 to 10.17; $P < 0.0001$).

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The Egger's test suggested no significant publication bias in the meta-analysis of mortality, gastric residual volume, adequate enteral nutrition achievement, and ventilator-associated pneumonia.
Conclusion: A greater gastric residual volume, more frequent vomiting, and greater incidences of ventilator-associated pneumonia and enteral feeding interruptions are linked to enteral nutrition during prone ventilation. There was no statistically significant difference in mortality between the prone and supine positions. However, the prone position showed a slight trend toward reducing energy achievement rates, although this difference was not statistically significant.
Trial registration number: PROSPERO CRD: 42023441409.

Keywords
Prone ventilation, enteral nutrition, supine position

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Introduction

Since the 1970 s, multiple studies have indicated that prone positioning (PP) enhances oxygenation in adults with acute respiratory distress syndrome (ARDS), reducing mortality and the duration of mechanical ventilation.[1–3] Prone ventilation (PV) was widely used in intensive care units (ICUs) during the coronavirus disease 2019 (COVID-19) pandemic to improve oxygenation in critically ill patients with predominantly hypoxic respiratory failure.[4,5] Critically ill patients receiving PV have increased metabolic demands.[6,7] Therefore, early nutritional support is essential.

Guidelines recommend that enteral nutrition (EN) is currently the preferred method for providing nutrition to critically ill patients.[8,9] EN promotes the recovery of gastrointestinal motility and digestive absorption function[9] as well as inhibits excessive immune responses by improving intestinal mucosal barrier function, thereby reducing the risk of infection.[10] Furthermore, early EN within 3 days of mechanical ventilation initiation in real-world practice has demonstrated improved clinical and economic outcomes.[11]

Providing EN to patients undergoing PV is associated with a range of complications, such as delayed gastric emptying, high gastric residual volume (GRV), vomiting, and reflux.[12] However, there is no evidence indicating that occasional mild elevations under monitored conditions (such as PP) lead to delayed gastric emptying. Reigner et al.[12] reported that patients treated in the prone position showed very poor tolerance of early EN compared with those treated in the supine position. However, Savio et al.[6] confirmed that there was no significant difference in these aspects between patients in the prone position and those in the supine position. The safety and efficacy of EN during PV is still not fully understood, and results from different studies have shown different trends; therefore, further research is needed.

Through a meta-analysis, we assessed the safety and efficacy of EN in patients undergoing PV. We examined factors such as high GRV, vomiting, ventilator-associated pneumonia (VAP), EN interruption, energy achievement rate, and mortality in patients undergoing PV. The results provide evidence-based insights into variations in the safety and efficacy of EN across studies, thus supporting clinical practice.

Methods

The prospective and retrospective studies protocol comprising objectives, literature search strategies, inclusion and exclusion criteria, outcome measurements, and statistical analysis methods was prepared a priori according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). We followed the PRISMA 2020 guidelines.[13]

Publication search strategy

All relevant literature was retrieved from PubMed, Embase, Cochrane Library, Web of Science, Cumulative Index of Nursing and Allied Health Literature, and WanFang Data databases from their inception to 24 December 2024. Specific search strategies can be found in the "text of search strategy." The studies were restricted to those conducted on humans. To identify potentially relevant studies, the abstracts and titles of all publications were first screened to select potentially suitable articles. Finally, the full texts were read to verify whether they met the inclusion criteria.

Exclusion and inclusion criteria

The following inclusion criteria were applied: (a) studies with a control group, including patients aged over 18 years who were undergoing PV and receiving EN; the experimental group received PV, whereas the control group received supine or semi-upright ventilation; (b) studies exploring clinical data and prognosis; (c) studies providing sufficient data to calculate odds ratio (OR); (d) studies reporting outcomes as hazard ratio (HR) with 95% confidence interval (CI); (e) studies for which full-text articles were available; and (f) prospective cohort studies. Furthermore, the exclusion criteria were as follows: (a) cancer cell studies, animal experiments, laboratory research, comments, reviews, letters, systematic reviews, meta-analyses, and conference abstracts; (b) studies that lacked a control group; and (c) studies providing insufficient data or too little information to obtain HR.

Data extraction

The data presented in this study included the first author's name, publication year, research type, number of patients undergoing PV and receiving EN as well as number of patients in the control group, high GRV, vomiting, VAP, incidence of EN interruption, energy achievement rate, and mortality rate.

Statistical analysis

Statistical analyses were performed using Review Manager 5.4 and Stata 17. OR (HR) with 95% CI were calculated to examine the relationships between PV, EN, clinical outcomes, and complications. Heterogeneity was assessed using I^2 value of $>50\%$ or Q statistic P-value of <0.10; fixed-effects models were used in case of absence of heterogeneity, otherwise random-effects models were applied. Publication bias was evaluated using the Egger's test ($P < 0.05$ indicating significance).

Results

Search results and study characteristics

The process of study selection is visually represented in Figure 1.

The flowchart outlines the identification of 81 studies from multiple databases. After removing 17 duplicate studies, 64 titles and abstracts were screened, thereby excluding 39 studies. Full texts of 25 studies were reviewed, and five studies were finally included in the meta-analysis for quantitative synthesis. Therefore, five articles with 319 patients were included, and the relevant data were extracted.[12,14–17] The characteristics and quality assessment of the included studies are detailed in Table 1.

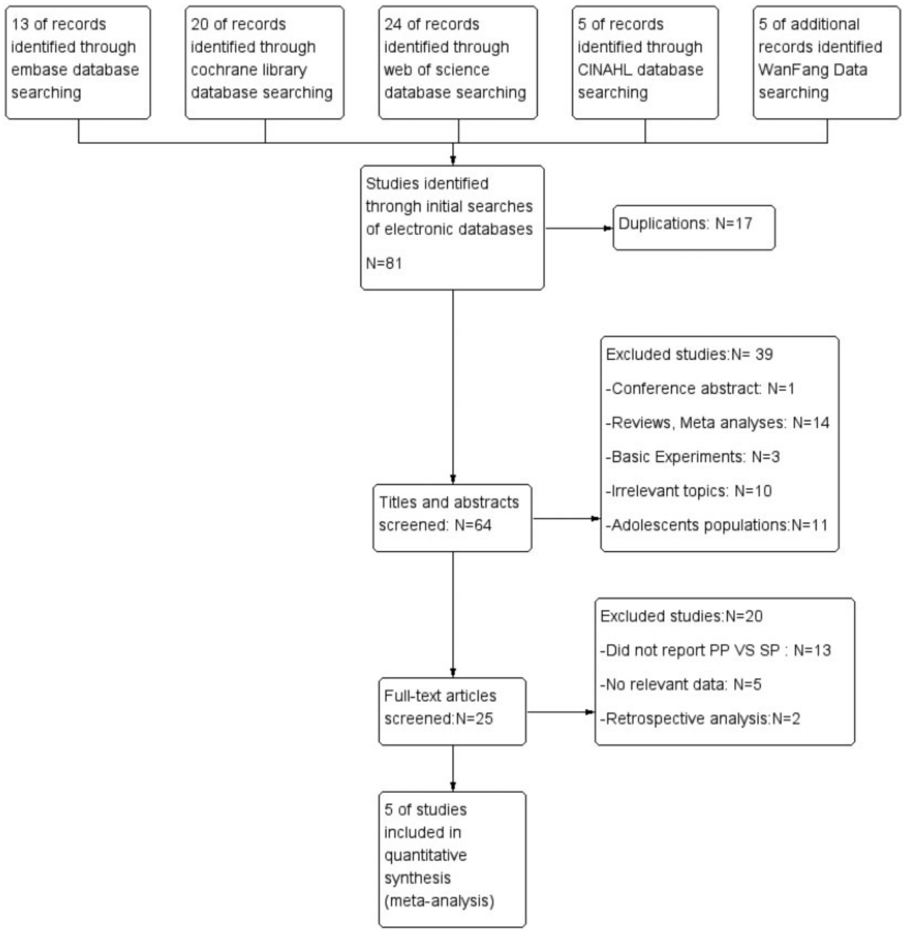

Figure 1. Flowchart of the selection of studies for inclusion in the study.

Table 1 summarizes seven studies that explored the safety and efficacy of EN in patients undergoing PV. The study participants included critically ill patients with ARDS, COVID-19, and community-acquired pneumonia, with sample sizes ranging from 19 to 126 patients. Most patients underwent PV in the ICU and received nasogastric tube feeding, with some of them also receiving gastrointestinal prokinetic medications. The studies generally monitored GRV, setting thresholds at >0.15, >0.25, and >0.5 L, and the feeding was discontinued when these limits were exceeded. EN doses were adjusted according to the patient's conditions, gradually increasing from 30 kcal/kg per day.

Efficacy analysis showed no significant difference in mortality between prone and supine positions (OR: 1.11; 95% CI: 0.65 to 1.88; $P = 0.70$) (Figure 2). Furthermore, there was no heterogeneity between three studies.[12,16,17] After the analysis of four studies,[12,15–17] the prone position appeared to slightly reduce the energy achievement rates (mean difference: −0.88; 95% CI: −1.83 to 0.06; $P = 0.07$); however, the difference was not statistically significant. The high heterogeneity ($I^2 = 94\%$) suggested variability in study results. These findings

Table 1. Characteristics and quality assessment of all included studies.

Name	Year	Design	Sample	Disease condition	Interventions	Nutritional support plan	Management of EN intolerance	Outcomes	HGR	NOS score
Van der Voort et al.	2001	POS	19	APACHE II: 25.5 ± 8.9 points Study duration: 12 h	Patients alternated every 6 h PP/6 h SP. Compared in the same patient	Enteral feeding (0.08 L/h) as the nutritional target, without PPI	10 patients received cisapride for GRV pre-study. GRV > 0.15L	Enteral feeding can be continued	GRV>0.15L	7
Reignier et al.	2004	PCS	71	Received ventilation with early EN for 5 days Study duration: 5 days	PP turned every 6 h, gastric volume monitored every 6 h	Gradual increase in EN from 0.5 L on day 1 to 2 L on days 4–5	Stop feeding when GRV reaches >0.25 L or vomiting occurs, resume feeding slowly with prokinetics	GRV, vomiting, VAP, mortality, early EN are poorly tolerated	GRV > 0.25 L	7
Liu et al.	2006	PCS	69	Patients on MV Study duration: 5 days	Continuous SP (n = 35) or PP (n = 34) for severe hypoxemia and early EN	Day 1: 0.03 L/h, increase by 0.03 L/h daily until day 4. EN: 0.5 L (day 1) to 2 L (days 4–5)	Monitor the residual volume of the gastro-intestinal tract and stop EN when GRV reaches >0.15 L, prokinetics	MV in PP, poor EN Tolerance. Enteral nutrition volume and GRV	GRV > 0.15 L	8
Saez de la Fuente et al.	2014	PCO	34	High severity (60% APACHE II >15) Common diagnosis: CAP ICU stay (29.9 ± 19.3 days)	PP for severe hypox-emia, compared with SP in the same patient	EN via nasogastric tube target (25 kcal/kg/day) Monitor GI complications PN used in case of underfeeding	GRV: consider using decision tree. Vomiting and diet regurgitation: stop feeding when GRV reaches >0.5 L Assess and resume feed-ing after correction	No significant differ-ences in complica-tion GRV, vomiting, regurgitation	GRV > 0.5 L, no specific number of people	8
J. A. de Paula et al.	2022	PCS	126	Patients with COVID-19 receiving EN on MV, who needed or did not need PP	PP turned every 6 h, gastric volume monitored every 6 h	Week 1: 15–20 kcal/kg/day Rehabilitation phase: 30 kcal/kg/day	Adjust rates and proki-netics, stop feeding, monitor GRV, address vomiting	Days on MV, ICU stay, hospital stay, VAP and mortality Prone EN can be safe	Not mentioned	8
Total			319							

EN: enteral nutrition; HGR: high gastric residuals; NOS: Newcastle–Ottawa Scale; POS: prospective observational study; APACHE: Acute Physiology and Chronic Health Evaluation; PP: prone position; SP: supine position; PPI: proton pump inhibitor; GRV: gastric residual volume; PCS: prospective comparative study; VAP: ventilator-associated pneumonia; MV: Mechanical ventilation; PCO: prospective cross-over; GI: gastrointestinal; PN: parenteral nutrition; CAP: community-acquired pneumonia; COVID-19: coronavirus disease 2019

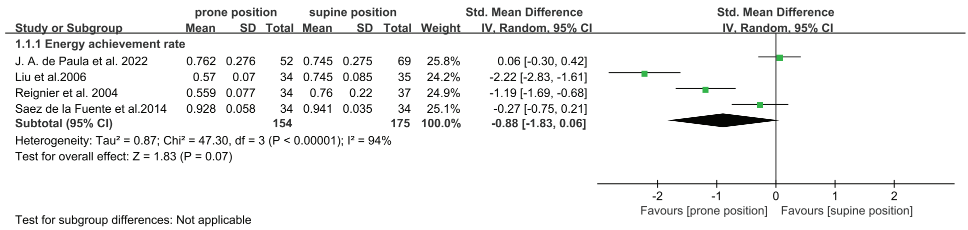

Figure 2. Prone vs. supine position with enteral nutrition: comparative analysis of energy achievement rates in medical studies.

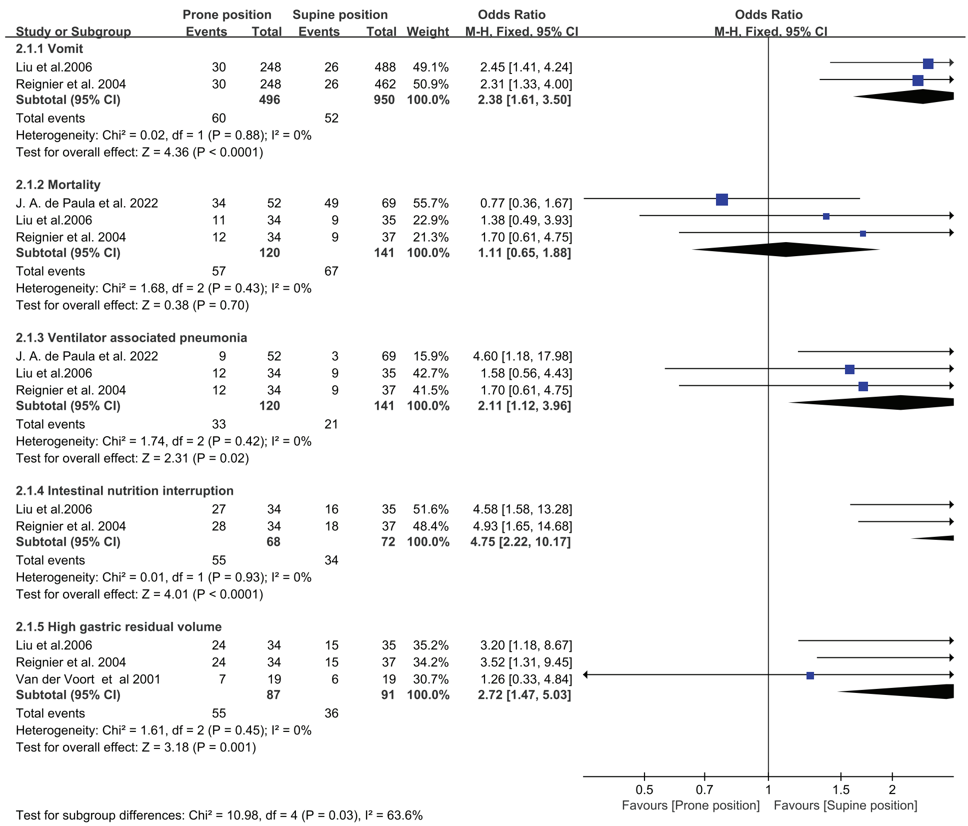

Figure 3. Prone vs. supine position with enteral nutrition: comparative analysis of clinical outcomes across multiple medical studies.

imply that although the prone position may be necessary for certain clinical conditions, its impact on EN efficacy remains inconclusive and warrants further investigation.

Furthermore, safety analysis revealed that the prone position significantly increased the risk of high GRV (OR: 2.72; 95% CI: 1.47 to 5.03; P = 0.001) (Figure 3). Two studies[14,17] used GRV $\geq$ 0.15 L as the criterion for high GRV, whereas one study[12] used GRV $\geq$ 0.25 L as the criterion. There was no heterogeneity between studies

($P = 0.45$, $I^2 = 0\%$), and a fixed-effects model was used for analysis. Two studies[12,17] reported the effect of EN on vomiting or intestinal nutrition interruption in patients during prone and supine positioning for ventilation. The heterogeneity test revealed that there was no heterogeneity between studies ($I^2 = 0$), and a fixed-effects model was used for analysis. The results showed that EN in the prone position increased the risk of vomiting (OR: 2.38; 95% CI: 1.61 to 3.50; $P < 0.0001$) and intestinal nutrition interruption (OR: 4.75; 95% CI: 2.22 to 10.17; $P < 0.0001$). These results suggest that EN in the prone position is associated with a higher risk of gastrointestinal complications than that in the supine position.

Three studies[12,16,17] reported the effect of EN on the incidence of VAP during ventilation in prone and supine positions. The heterogeneity test showed no heterogeneity between studies, and a fixed-effects model was used for analysis. The results indicated that EN in the prone position increased the risk of VAP (OR: 2.11; 95% CI: 1.12 to 3.96; $P = 0.02$).

Publication bias

For the included articles presented in Figure 4, we analyzed publication bias for all clinical characteristics using Egger's test. The findings suggested that there was no significant publication bias in the meta-analysis of mortality, GRV, VAP, and adequate EN achievement.

Discussion

Study quality and methodological limitations

This study included five prospective controlled trials. As the intervention involved position changes, blinding of both participants and researchers was not possible. However, as the outcome measures were all objective, the impact of blinding on the results was minimal. Additionally, the study compared the duration of prone and supine positioning within the same participants, making randomization unfeasible. All studies clearly defined the inclusion criteria for participants, ensuring comparability between groups. Comparing prone and supine positioning within the same individuals also helped reduce heterogeneity. The five studies had NOS scores of 7–8, indicating good evidence quality. However, we found that there were relatively few studies included in our research, and none of them addressed the type of EN management that can reduce the risks associated with EN during PV. The results should be interpreted with caution, and we hope that more high-quality clinical studies with larger sample sizes will be conducted in the future.

Efficacy of EN during PV and safety concerns

Expert consensus and societal guidelines recommend PP for the management of patients with severe ARDS.[18] The COVID-19 pandemic has led to PP being at the forefront of medicine, widely implemented in the management of severe ARDS and acute hypoxemic respiratory failure.[19] Moreover, guidelines strongly recommend early EN support for patients undergoing PV.[20] Although our study shows no significant difference in mortality regarding the efficacy of EN during PV, we hypothesize that although PP improves oxygenation, its effect on mortality can be influenced by various other clinical factors. The impact of EN on mortality in critically ill patients may be limited due to factors such as multiorgan dysfunction and intestinal dysfunction. Additionally, our study indicated that EN during PV slightly reduces energy absorption, which may be related to the slower infusion rate of EN when in the prone position.

Mortality

Number of studies = 3 Root MSE = .3284

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	-2.246354	.6218752	-3.61	0.172	-10.14803	5.65532
bias	5.049117	1.323388	3.82	0.163	-11.76612	21.86435

Test of H0: no small-study effects P = 0.163

Gastric residual volume

Number of studies = 3 Root MSE = .099

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	3.973157	.2342333	16.96	0.037	.9969404	6.949373
bias	-5.457486	.426363	-12.80	0.050	-10.87494	-.040031

Test of H0: no small-study effects P = 0.050

Ventilator-associated pneumonia

Number of studies = 3 Root MSE = .1211

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	-2.734081	.3216412	-8.50	0.075	-6.820919	1.352758
bias	6.130498	.5660569	10.83	0.059	-1.061937	13.32293

Test of H0: no small-study effects P = 0.059

Achieving adequate enteral nutrition

Number of studies = 4 Root MSE = 1.856

Std_Eff	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
slope	3.31544	1.152205	2.88	0.103	-1.642099	8.272978
bias	-16.9693	4.884943	-3.47	0.074	-37.98751	4.048913

Test of H0: no small-study effects P = 0.074

Figure 4. Egger's tests for mortality, gastric residual volume, ventilator-associated pneumonia, and achieving adequate enteral nutrition.

Increased GRV is an important factor affecting EN in critically ill patients.[21] Three articles in this study reported the impact of EN on high gastric residuals (HGR) during supine ventilation and PV. However, the thresholds for GRV varied, and the criteria for assessing HGR differed across studies. The findings showed that

EN during PV increases the incidence of HGR. Another research showed that excessively HGR increases the risk of aspiration, secondary infections, and mortality.[22] GRV helps assess EN tolerance and enables rapid formula adjustments.[23] In mechanically ventilated patients, measuring the GRV can also prevent medical complications such as vomiting.[24] Additionally, our study suggested that EN during PV increases the incidence of vomiting and EN interruptions. Our research highlights the need for further investigation into the safe management of EN in prone-ventilated patients as well as individual risk factors for patients in the prone position.[9,19,25]

Another aspect of safety in our study is related to infections. EN during PV increases the risk of aspiration pneumonia. There have also been some previous studies on aspiration pneumonia. One study found no increased VAP risk in the prone position, possibly due to improved clearance of respiratory secretions.[26] However, EN may increase VAP risk through reflux aspiration. A previous study showed that a high GRV is associated with aspiration.[27] A GRV over 0.2 L increases aspiration risk to 40%, with aspiration pneumonia being a common result.[28,29] Therefore, monitoring GRV and managing risk factors are essential to minimize aspiration pneumonia in critically ill patients receiving PV and EN.

Comparison with previous studies and future research needs

Several previous reviews have also explored the safety and efficacy of EN in patients undergoing PV. A review by Bruni et al.[30] revealed that patients in both positions had similar rates of VAP and mortality and a similar length of stay in ICU. However, a higher number of cases of EN cessation and vomiting occur during PP. No meta-analysis has yet been conducted on these findings. Therefore, we conducted a meta-analysis of five articles to further explore the safety and efficacy of EN during PV. Zhu et al.[31] analyzed five retrospective studies including children. There was an error in classifying observational studies as randomized controlled trials, and each study had different experimental and control groups, Notably, one study used the duration of prone and supine positioning as the sample size, which significantly differed from other studies that used the number of patients as the sample size. Yong et al.[32] concluded that post-pyloric feeding is better tolerated and safer than gastric feeding in patients undergoing PV. However, they did not analyze the efficacy and safety of EN in prone-ventilated patients compared with those receiving EN in the supine position.

Compared with previous studies, our research provides the latest cohort study data, and the five analyzed studies cover different populations such as patients with ARDS and COVID-19. All studies have focused on adults, and the articles have been rigorously selected, resulting in high quality and low heterogeneity.

Conclusion

Our meta-analysis provides evidence that PV combined with EN does not significantly affect mortality. Moreover, PV combined with EN is associated with an increased incidence of high GRV, vomiting, EN interruption, and VAP. However, the overall impact on patient outcomes remains unclear. Future research is warranted to optimize EN management in prone-ventilated patients and minimize risks such as aspiration and feeding interruptions. Large-scale, high-quality studies are needed to confirm these findings.

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Author contributions

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Supervision: Jianzhen Pan, Jianghong Zhao, and Fei Chen.
Validation: Jianzhen Pan, Lili Chen, and Gu Mei.
Visualization: Jianzhen Pan, Jianghong Zhao, and Fei Chen.
Writing—original draft: Jianzhen Pan, Jianghong Zhao, Lili Chen, and Gu Mei.
Writing—review & editing: Jianzhen Pan, Fei Chen, and Gu Mei.

Data availability statement

The data supporting the findings of this study are available within the article.

Declaration of conflicting interests

The authors report no conflicts of interest.

Ethical compliance

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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