

# Efficacy and Safety of a Combination of Enteral and Parenteral Nutrition Support in the Postoperative Period for Patients with Gastrointestinal Cancer: A Systematic Review and Meta-Analysis

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**Background:** Postoperative nutritional support in gastrointestinal cancer, including enteral nutrition (EN), parenteral nutrition (PN), and combined nutrition strategies, is vital for enhancing recovery and patient outcomes.

**Aims:** We aimed to comprehensively evaluate the impact of postoperative EN, PN, and EN + PN in patients with gastrointestinal cancer.

**Methods:** PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wan Fang, and VIP were searched from conception until January 2, 2024. Randomized controlled trials (RCTs) that compared different postoperative nutritional support (EN, PN, or EN + PN) in patients with gastrointestinal cancer were included. The Cochrane Risk of Bias Assessment tool was used to assess the quality of the RCTs. Fixed- and random-effects models were chosen according to the heterogeneity of variables for the synthesis of results. Continuous and categorical variables

were analyzed using the weighted mean difference or relative risk (RR) and 95% confidence interval (CI).

**Results:** In this meta-analysis, 11 RCTs were included. The PN + EN group exhibited significantly improved postoperative recovery, nutritional function, and immune indicators than the PN and EN groups ( $p < 0.05$ ). Additionally, a higher incidence of postoperative complications such as abdominal distension (RR: 2.53; 95% CI: 1.17-5.49), nausea/vomiting (RR: 2.01; 95% CI: 1.09-3.71), and diarrhea (RR: 3.17; 95% CI: 1.41-7.10) was observed in the EN group than in the PN + EN group.

**Conclusion:** Combining supplemental PN with enteral support improves energy intake and prognosis in gastrointestinal cancer, though limited studies restrict publication bias evaluation.

## INTRODUCTION

Recognized as one of the most prevalent and fatal types of cancer, gastrointestinal cancer imposes a burden on health and economics.<sup>1</sup> Statistics indicate that gastrointestinal cancers contribute to a quarter of all cancer incidences and a third of cancer-related fatalities globally.<sup>2</sup> Gastrointestinal cancers are recognized as consumptive diseases, which are frequently accompanied by malnutrition and impaired immune function when the patient is in a state of high catabolism for a prolonged period.<sup>3</sup> Surgical resection is typically the foundation of radical therapy for gastrointestinal cancers.<sup>4</sup> However, surgical resection can often result in significant

nutritional deficiencies due to limited food intake, poor digestion, and malabsorption.<sup>5</sup> Postoperative malnutrition increases the risk of infection, delays wound healing, and may be associated with a poor overall survival rate and recurrence-free survival rate in patients with gastrointestinal cancer.<sup>6,7</sup> The nutrition of patients can significantly affect the recovery and prognosis of patients with gastrointestinal cancer.<sup>8</sup> Thus, appropriate postoperative nutritional assistance is critical for the management of patients with gastrointestinal cancer.

Postoperative nutritional support for patients with gastrointestinal cancers can be provided via several methods, including enteral nutrition (EN), parenteral nutrition (PN), and a combination of both



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(EN + PN).<sup>9</sup> Generally, providing nutrients directly into the digestive tract via a percutaneous endoscopic gastrostomy or nasogastric tube is defined as EN.<sup>10</sup> EN is frequently regarded as the optimum nutritional support in clinics because it promotes immune function, preserves gut integrity, and lowers the risk of infection.<sup>11</sup> PN is a form of nutritional therapy that involves the intravenous administration of nutrients. PN is regarded as a crucial approach to preventing malnutrition in specific patients in whom the gastrointestinal tract is impaired or fails to meet nutritional requirements.<sup>12</sup> However, both methods are associated with some disadvantages. Patients receiving PN are prone to bacterial translocation, surgical problems, and poor recovery,<sup>13</sup> whereas patients receiving EN are prone to food intolerance.<sup>14</sup> Feeding intolerance, which often manifests as gastrointestinal symptoms (e.g., large gastric residual volume, vomiting, bloating, and diarrhea), interferes with the effective absorption of nutrients and exacerbates malnutrition.<sup>15</sup> The European Society for Parenteral and Enteral Nutrition guidelines for the intensive care unit explicitly state that when a patient's nutritional demands cannot be addressed with EN, PN should be administered as a supplement.<sup>16</sup> Furthermore, studies have demonstrated that supplementing PN with EN significantly improves energy intake and prognosis.<sup>17,18</sup> Thus, the combination of EN and PN might be the optimal clinical nutritional support.

Previous studies have reported inconsistent results of the three nutritional supports (EN, PN, and EN + PN) in terms of postoperative recovery, complication rates, and overall survival. For instance, Wang et al.<sup>19</sup> discovered that there was no difference in the duration of hospital stay among patients with gastrointestinal cancer who received different nutritional supports (PN vs. EN + PN). However, another study<sup>20</sup> conducted in patients 3 months after surgery determined that the patients in the EN + PN group exhibited superior physical function and energy/fatigue scores than the patients in the EN group. Most current studies have focused on the efficacy of a single nutritional support during the postoperative period in patients with gastrointestinal cancer. Furthermore, existing evidence on the postoperative efficacy of EN, PN, and EN + PN in patients with gastrointestinal cancer is inconsistent, and there is a lack of comprehensive evaluation studies. Therefore, herein, we conducted a meta-analysis of various randomized controlled trials (RCTs) that have investigated postoperative nutritional support (PN, EN, and EN + PN) in patients with gastrointestinal cancer. Our study findings may contribute to a more thorough assessment of the efficacy of nutritional support (PN, EN, and EN + PN) during the postoperative period in patients with gastrointestinal cancer, providing physicians with a foundation for selecting the best nutritional support.

## MATERIALS AND METHODS

### Literature screening

The literature was systematically reviewed according to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)<sup>21</sup> and the Cochrane Handbook for Systematic Reviews of Intervention.<sup>22</sup> PubMed, Embase, Cochrane Library, Web

of Science, the China National Knowledge Infrastructure, Wanfang Data, and the China Science and Technology Journal Database were searched from inception to January 2, 2024. The searches were conducted using a combination of subject terms and free words (Supplementary Table 1).

### Inclusion and exclusion criteria

Based on the Population, Intervention, Comparison, Outcomes and Study principles,<sup>23</sup> the following comprehensive inclusion criteria were outlined:

- **Participants:** Patients with gastrointestinal cancer who had undergone surgical treatment.
- **Interventions and comparisons:** Studies comparing different postoperative nutritional support (EN, PN, or EN + PN).
- **Outcomes:** Postoperative recovery indicators that included the time-to-first flatus, time-to-first feces, and duration of hospital stay. Nutritional indicators that included albumin (ALB), prealbumin (PA), transferrin (TF), and hemoglobin (HGB) levels. Immunological indicators that included immunoglobulin A (IgA), IgG, IgM, cluster of differentiation 3 (CD3<sup>+</sup>), CD4<sup>+</sup>, and CD8<sup>+</sup> levels, as well as CD4<sup>+</sup>/CD8<sup>+</sup> ratios. Postoperative complications that included abdominal pain, abdominal distension, diarrhea, nausea/vomiting, surgical wound infection, and anastomotic fistula.
- **Study design:** All RCTs were included.

Studies with the following characteristics were excluded from the analysis: animal experiments, review/literature review, note, conference abstract, expert consensus, guidelines, trial, registry record, meta-analysis, study protocol, letter, editorial, summary, conference paper, short survey, and articles not relevant to the investigated topic.

### Data extraction

A flowchart based on PRISMA (Figure 1) was utilized to illustrate the literature search process, including the screening process, exclusion criteria, and the specific number of articles. First, duplicate studies were removed using EndNote X9. Thereafter, two reviewers independently screened the abstracts of the retrieved articles to ensure that all the included studies were relevant. Subsequently, the full texts of the studies were screened by two reviewers. In the case of studies conducted by the same authors and involving the same study populations, only those with complete data were selected to avoid data duplication. Two reviewers independently gathered data from the eligible studies. Any disagreements were discussed and resolved via consultation with a third reviewer. A predetermined questionnaire was utilized to extract the following relevant data: i) fundamental details of the included studies such as article title, authors, and publication year; ii) basic characteristics of the study participants such as sample size, age, and sex distribution; iii) specific intervention particulars, including intervention content and duration; and iv) outcome indicators and the corresponding measurement data.

### **Evaluation of the literature quality**

The Cochrane Collaboration Tool<sup>24</sup> was used to assess the quality of the RCTs. The included studies were scored on the basis of the following seven items: randomization sequence generation,

allocation concealment, double blinding of investigators and participants, blinding of outcome assessment, incomplete outcome data, selective publication, and other biases.

**TABLE 1.** The Characteristics of the Included Studies.

First author	Year	Country	Study design	Population	Intervention	n	Male/female	Age (year)	Course of treatment (day)
Chen	2019	China	RCT	Elderly patients with colorectal cancer after surgery	PN	50	32/18	67.2 0±5.10	7
					EN + PN	50	34/16	67.60±5.20	7
Li	2015	China	RCT	Undergoing surgical therapy for gastric cancer	PN	45	25/20	62.50±5.30	7
					EN + PN	45	25/20	62.50±5.30	7
Huang	2015	China	RCT	Old patients receiving surgery for GI cancer	PN	35	NA	66.10±8.10	7
					EN	35	NA	66.70±7.20	7
					EN + PN	35	NA	67.20±7.90	7
Liu	2009	China	RCT	Elderly gastric cancer patients after surgery	PN	50	NA	NA	7
					EN	51	NA	NA	7
					EN + PN	52	NA	NA	7
Peng	2010	China	RCT	Colon cancer surgery patient	PN	32	18/14	63.74±10.34	7
Chen	2013	China	RCT	Patients with gastric cancer after radical surgery	EN + PN	32	18/14	63.43±10.13	7
					PN	34	19/15	51.00±5.90	7
Liu	2013	China	RCT	Elderly gastric cancer patients after surgery	EN + PN	34	21/13	51.00±9.80	7
					PN	44	26/18	74.20±7.60	7
Ma	2018	China	RCT	Surgical resection of colorectal cancer patients	EN + PN	43	29/14	75.80±5.50	7
					PN	53	26/27	55.90±10.80	7
					EN	53	29/24	56.40±12.30	7
Xie	2023	China	RCT	Patients undergoing radical gastrectomy	EN + PN	53	28/25	57.40±9.70	7
					EN	60	34/26	43.79±8.36	7
					EN + PN	60	32/28	45.36±8.28	7
Hao	2023	China	RCT	Patients undergoing radical gastrectomy	EN	34	19/15	51.73±7.45	7
					EN + PN	34	21/13	51.86±8.30	7
Gao	2023	China	RCT	Colorectal cancer patients undergoing radical surgery	EN	50	27/23	52.39±4.02	7
					EN + PN	50	28/22	52.54±3.97	7

RCT, randomized controlled trial; EN, enteral nutrition; PN, parenteral nutrition; N, number of samples; NA, not applicable.

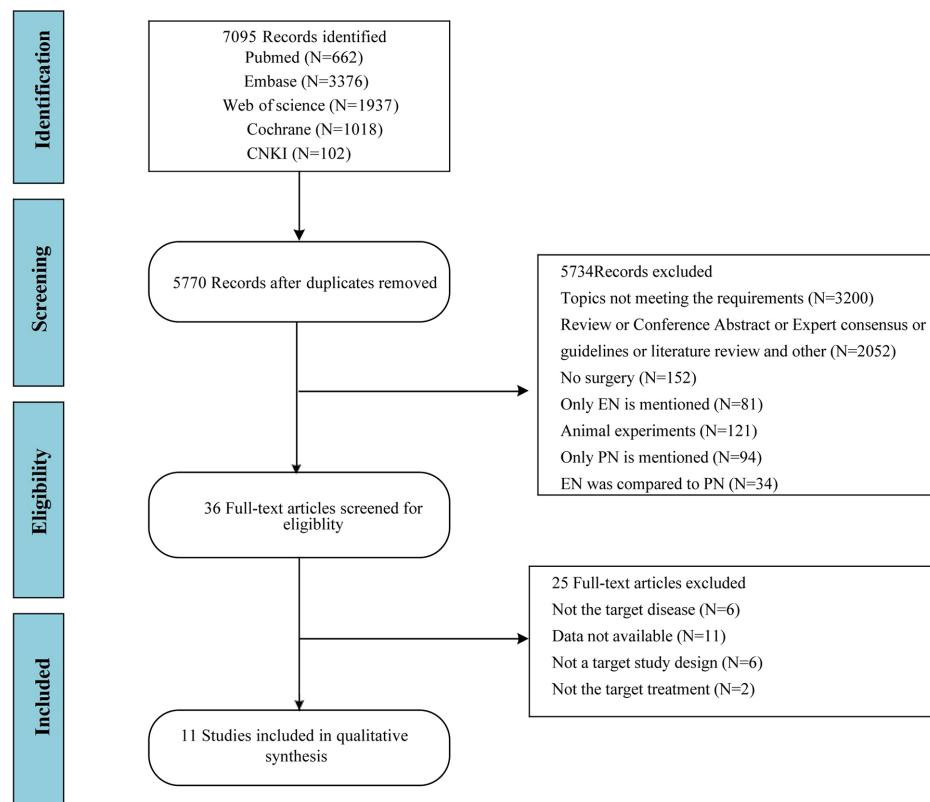
### Statistical analysis

The weighted mean difference (WMD) was employed as the effect indicator for the continuous variables, whereas the relative risk (RR) was utilized for the categorical variables. The effect sizes were subsequently expressed as 95% confidence intervals (CIs). Heterogeneity was assessed separately for each outcome variable using the statistical value  $I^2$ . If the  $I^2$  was  $> 50\%$ , a random-effects model was utilized. If the  $I^2$  was  $< 50\%$ , a fixed-effects model was employed. Sensitivity analyses were conducted using the leave-one-out approach, excluding the study with the highest risk of bias or the smallest sample sizes, to ensure that the findings remained robust. Statistical analyses were performed using Stata (version 15.1). In addition, RevMan (version 5.3) was employed to generate the risk of bias plots and summary plots, which were used to assess the quality of RCTs. Statistical significance was determined at a two-tailed  $p$  value of  $< 0.05$ .

## RESULTS

### Characteristics of the eligible studies

Initially, 7,095 records were retrieved from the databases using the search strategy. After eliminating duplicates and reviewing the titles and abstracts, 36 studies were selected for full-text verification. Finally, 11 studies (Supplementary material of included literature) were included in the meta-analysis (Figure 1).



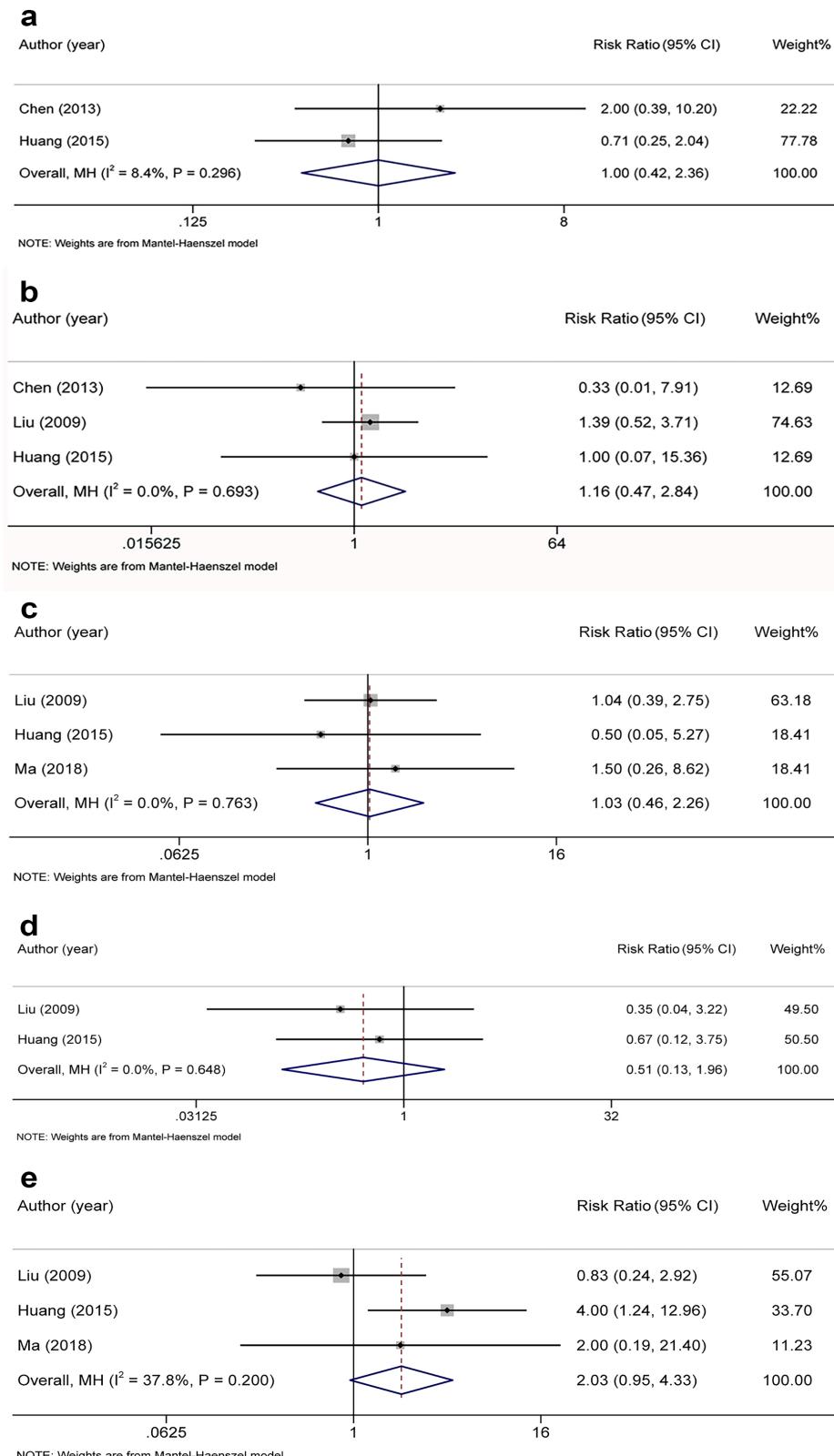
**FIG. 1.** Flow chart of the process of study selection.

EN, enteral nutrition; PN, parenteral nutrition.

Table 1 presents the characteristics of the enrolled studies. The 11 included studies were all RCTs and had been published between 2009 and 2023. The sample sizes of the studies varied from 32 to 60, exhibiting a close approximation. The standard treatment course lasted for 7 days, and the average age of the study participants ranged from 43.79 to 75.80 years. All the included studies focused on patients with gastric cancer and colorectal cancer. In three of the 11 studies, all three postoperative nutritional support therapy (EN, PN, and EN + PN) were compared. In five studies PN was compared with EN + PN, while in three studies, EN was compared with EN + PN.

### Quality evaluation and research bias

To evaluate the bias for each study, risk of bias plots and summary plots were generated. Incomplete outcome data and blinding of outcome assessment were considered a low risk of bias, while allocation concealment was considered a high risk of bias (Supplementary Figure 1). After summarizing the risk of bias for the included studies (Supplementary Figure 2), we found that the study by Liu<sup>25</sup> exhibited the highest risk of bias. Most of the other studies exhibited a risk bias level of two items. In general, the risk of bias in the meta-analysis was acceptable.



**FIG. 2.** Postoperative complication indicators in the PN and EN + PN groups: (a) abdominal pain, (b) abdominal distension, (c) nausea/vomiting, (d) diarrhea, and (e) surgical wound infection.

CI, confidence interval; EN, enteral nutrition; PN, parenteral nutrition.

### **Comparison of postoperative PN and EN + PN in patients with gastrointestinal cancer**

The postoperative recovery indicators were compared between the PN and EN + PN groups. Because the heterogeneity among the studies was significant ( $I^2 > 50\%$ ), a random-effects model was used for the combined effect analysis of the postoperative indicators. The time-to-first flatus, time-to-first feces, and duration of hospital stay were longer in the PN group than in the EN + PN group (Table 2). The WMD of the time-to-first flatus, time-to-first feces, and duration of hospital stay were 1.63 (95% CI: 1.41-1.86), 1.07 (95% CI: 0.82-1.33), and 1.16 (95% CI: 0.96-1.36), respectively ( $p < 0.001$  for all).

The postoperative nutritional functioning were compared between the PN and EN + PN groups using the ALB, PA, TF, and HGB levels. A fixed-effects model was used to analyze the HGB levels ( $I^2 = 50\%$ ), while a random-effects model was used to analyze the ALB, PA, and TF ( $I^2 > 50\%$ ). The PN group exhibited lower levels of ALB, PA, and TF ( $p < 0.05$ ) than the EN + PN group (Table 2). However, there was no difference in the HGB levels between the two groups (WMD: 0.13; 95% CI: -0.20 to 0.47).

A random-effects model was used to analyze the immune indicators, except the CD4<sup>+</sup>/CD8<sup>+</sup> ratio ( $I^2 = 20.2\%$ ), between the PN and EN + PN groups (Table 2). The levels of IgA (WMD: -0.72), IgG (WMD: -0.53), IgM (WMD: -0.83), CD3<sup>+</sup> (WMD: -1.56), and CD4<sup>+</sup> (WMD: -0.93), and the CD4<sup>+</sup>/CD8<sup>+</sup> ratio (WMD: -0.54) were lower in the PN group than in the EN + PN group (all  $p < 0.05$ ). However, there was no difference in the C3 (WMD: 0.25; 95% CI: -0.59 to 0.10) and CD8<sup>+</sup> (WMD: 0.04; 95% CI: -0.24 to 0.16) levels between the two groups.

To investigate the safety of alternative postoperative nutritional therapies, the incidences of postoperative complications in the two groups were compared (Figure 2). The heterogeneity of the studies within each subgroup ( $I^2 < 50\%$ ) did not exhibit any differences. Thus, a fixed-effects model was used for the meta-analysis. There were no differences in the postoperative complications (nausea/vomiting, diarrhea, surgical wound infection, abdominal discomfort, and abdominal distension) between the two groups (all  $p > 0.05$ ).

### **Comparison of postoperative EN and EN + PN in patients with gastrointestinal cancer**

Table 3 demonstrates the postoperative recovery of the EN and EN + PN groups. The random-effects model ( $I^2 > 50\%$ ) revealed that the time-to-first flatus, time-to-first feces, and duration of hospital stay were shorter in the EN+PN group than in the EN group (all  $p < 0.001$ ).

The nutritional indicators were analyzed using random-effects models ( $I^2 > 50\%$ ; Table 3). The levels of ALB, PA, HGB, and TF were lower in the EN group than in the EN + PN group, with WMDs of -1.09 (95% CI: -1.27 to -0.91), -1.20 (95% CI: -1.40 to -0.99), -0.76 (95% CI: -1.09 to -0.44), and -0.60 (95% CI: -0.79 to -0.42), respectively.

In the analysis of immunological indicators, sufficient data were collected for the analysis of only CD3<sup>+</sup> and CD4<sup>+</sup> levels and the CD4<sup>+</sup>/CD8<sup>+</sup> ratio (Table 3). The random-effects models demonstrated that the CD3<sup>+</sup> level ( $I^2 = 90.7\%$ ; WMD: -0.71; 95% CI: -0.95 to -0.47) and

CD4<sup>+</sup>/CD8<sup>+</sup> ration ( $I^2 = 92.4\%$ ; WMD: -0.84; 95% CI: -1.08 to -0.59) were significantly lower in the EN group than in the EN + PN group. There was no statistically significant difference in the CD4<sup>+</sup> levels between the two groups ( $p > 0.05$ ).

The fixed-effects model ( $I^2 = 0\%$ ) revealed that the incidences of abdominal distension (RR: 2.53; 95% CI: 1.17-5.49), diarrhea (RR: 3.17; 95% CI: 1.41-7.10), and nausea/vomiting (RR: 2.01; 95% CI: 1.09-3.71) were higher in the EN group than in the EN + PN group (Figure 3). There was no difference in the risk of surgical wound infection and anastomotic fistula formation between the two groups ( $p > 0.05$ ).

### **Sensitivity analysis and publication bias**

There were no changes in the direction and margin of the composite estimates (Tables 2, 3), indicating that the results are stable and that individual studies did not excessively affect the results. In this meta-analysis, publication bias was not evaluated because each outcome included data from no more than ten studies.<sup>26</sup>

## **DISCUSSION**

To examine the efficacy and safety of postoperative nutritional support therapy (EN, PN, and EN + PN) in patients with gastrointestinal cancer, 11 RCTs were included in our meta-analysis. Our study results demonstrated the that postoperative recovery, nutritional status, and immune status of patients with gastrointestinal cancer were significantly better in the EN + PN group than in the EN or PN groups. However, there were significant differences in the postoperative complications only between the EN and EN + PN groups.

Typically, EN is more effective than PN in the postoperative recovery of patients with gastrointestinal malignancies.<sup>27,28</sup> A meta-analysis conducted by Yan et al.<sup>27</sup> demonstrated that EN can reduce the incidence of postoperative complications and length of hospital stay. Another meta-analysis comparing the efficacies of PN and EN demonstrated that patients treated with EN had shorter hospital stays, shorter time-to-flatus, and significantly increased ALB levels than patients who were administered total PN after abdominal surgery.<sup>28</sup> However, patients being treated with EN are prone to malnutrition due to EN intolerance.<sup>14</sup> A recent study suggested that postoperative recovery is significantly better with EN + PN administration than with EN or PN administration.<sup>29</sup> An observational cross-sectional study in 536 adult patients undergoing major gastrointestinal surgery demonstrated that the lowest caloric/protein deficiency was observed in those receiving EN + PN, followed by those receiving PN alone and those receiving EN alone.<sup>30</sup> Wu et al.<sup>20</sup> determined that early postoperative PN supplementation contributes to the patient's full caloric requirement, which may be associated with the supply of calories and protein. In a meta-analysis evaluating the effects of postoperative EN + PN and EN in patients with gastric cancer, the EN + PN group exhibited a shorter hospital stay and lower rate of postoperative complications than the EN group. However, there was no difference in the time-to-first flatus between the two groups.<sup>31</sup> Consistent with previous

**TABLE 2.** Comparing EN + PN with PN in Patients After Surgery for Gastrointestinal Cancer.

<b>Outcomes</b>	<b>Indicators</b>	<b>N of studies</b>	<b>WMD/RR (95% CI)</b>	<b>p</b>	<b>I<sup>2</sup> (%)</b>
<b>Complications</b>					
Abdominal pain	Overall	2	1.00 (0.42, 2.36)	1,000	8.4
	Sensitive analysis <sup>a</sup>	2	1.00 (0.42, 2.36)		
	Sensitive analysis <sup>b</sup>	2	1.00 (0.42, 2.36)		
	Sensitive analysis <sup>c</sup>	-	-		
Abdominal distension	Overall	3	1.16 (0.47, 2.84)	0.743	0.0
	Sensitive analysis <sup>a</sup>	3	1.16 (0.47, 2.84)		
	Sensitive analysis <sup>b</sup>	2	1.33 (0.53, 3.35)		
	Sensitive analysis <sup>c</sup>	2	0.50 (0.47, 5.39)		
Nausea/vomiting	Overall	3	1.03 (0.46, 2.26)	0.951	0.0
	Sensitive analysis <sup>a</sup>	3	1.03 (0.46, 2.26)		
	Sensitive analysis <sup>b</sup>	2	1.14 (0.49, 2.67)		
	Sensitive analysis <sup>c</sup>	2	1.00 (0.26, 3.89)		
Diarrhea	Overall	2	0.51 (0.13, 1.96)	0.327	0.0
	Sensitive analysis <sup>a</sup>	2	0.51 (0.13, 1.96)		
	Sensitive analysis <sup>b</sup>	2	0.51 (0.13, 1.96)		
	Sensitive analysis <sup>c</sup>	-	-		
Incision infection	Overall	3	2.03 (0.95, 4.33)	0.067	37.8
	Sensitive analysis <sup>a</sup>	3	2.03 (0.95, 4.33)		
	Sensitive analysis <sup>b</sup>	2	1.02 (0.34, 3.07)		
	Sensitive analysis <sup>c</sup>	-	-		
<b>Postoperative recovery</b>					
Time to first flatus	Overall	5	1.63 (1.41, 1.86)	<0.001	94.7
	Sensitive analysis <sup>a</sup>	5	1.63 (1.41, 1.86)		
	Sensitive analysis <sup>b</sup>	4	1.77 (1.51, 2.02)		
	Sensitive analysis <sup>c</sup>	4	1.34 (1.10, 1.57)		
Time to first feces	Overall	3	1.07 (0.82, 1.33)	<0.001	69.6
	Sensitive analysis <sup>a</sup>	3	1.07 (0.82, 1.33)		
	Sensitive analysis <sup>b</sup>	2	1.26 (0.96, 1.56)		
	Sensitive analysis <sup>c</sup>	-	-		
Duration of hospital stay	Overall	5	1.16 (0.96, 1.36)	<0.001	53.2
	Sensitive analysis <sup>a</sup>	5	1.16 (0.96, 1.36)		
	Sensitive analysis <sup>b</sup>	4	1.08 (0.86, 1.29)		
	Sensitive analysis <sup>c</sup>	4	1.30 (1.07, 1.53)		
<b>Nutritional indicators</b>					
ALB (g/L)	Overall	6	-0.21 (-0.39, -0.04)	0.016	90.0
	Sensitive analysis <sup>a</sup>	6	-0.21 (-0.39, -0.04)		
	Sensitive analysis <sup>b</sup>	5	-0.24 (-0.43, -0.05)		
	Sensitive analysis <sup>c</sup>	5	-0.45 (-0.65, -0.26)		
PA (mg/L)	Overall	4	-1.20 (-1.43, -0.97)	<0.001	91.9
	Sensitive analysis <sup>a</sup>	4	-1.20 (-1.43, -0.97)		
	Sensitive analysis <sup>b</sup>	3	-1.57 (-1.84, -1.31)		
	Sensitive analysis <sup>c</sup>	-	-		

**TABLE 2.** Continued

<b>Outcomes</b>	<b>Indicators</b>	<b>N of studies</b>	<b>WMD/RR (95% CI)</b>	<b>p</b>	<b>I<sup>2</sup> (%)</b>
TF (g/L)	Overall	5	-0.42 (-0.61, -0.23)	<0.001	87.5
	Sensitive analysis <sup>a</sup>	5	-0.42 (-0.61, -0.23)		
	Sensitive analysis <sup>b</sup>	4	-0.52 (-0.73, -0.31)		
	Sensitive analysis <sup>c</sup>	4	-0.56 (-0.78, -0.34)		
HGB (g/L)	Overall	2	0.13 (-0.20, 0.47)	0.439	0.0
	Sensitive analysis <sup>a</sup>	2	0.13 (-0.20, 0.47)		
	Sensitive analysis <sup>b</sup>	2	0.13 (-0.20, 0.47)		
	Sensitive analysis <sup>c</sup>	-	-		
<b>Immunological indicators</b>					
IgA	Overall	6	-0.72 (-0.90, -0.54)	<0.001	77.3
	Sensitive analysis <sup>a</sup>	6	-0.72 (-0.90, -0.54)		
	Sensitive analysis <sup>b</sup>	5	-0.74 (-0.94, -0.55)		
	Sensitive analysis <sup>c</sup>	-	-		
IgG	Overall	6	-0.53 (-0.70, -0.35)	<0.001	86.6
	Sensitive analysis <sup>a</sup>	6	-0.53 (-0.70, -0.35)		
	Sensitive analysis <sup>b</sup>	5	-0.53 (-0.72, -0.33)		
	Sensitive analysis <sup>c</sup>	-	-		
IgM	Overall	6	-0.83 (-1.01, -0.65)	<0.001	58.6
	Sensitive analysis <sup>a</sup>	6	-0.83 (-1.01, -0.65)		
	Sensitive analysis <sup>b</sup>	5	-0.91 (-1.10, -0.71)		
	Sensitive analysis <sup>c</sup>	-	-		
C3	Overall	2	-0.25 (-0.59, 0.10)	0.160	66.3
	Sensitive analysis <sup>a</sup>	2	-0.25 (-0.59, 0.10)		
	Sensitive analysis <sup>b</sup>	2	-0.25 (-0.59, 0.10)		
	Sensitive analysis <sup>c</sup>	-	-		
CD3 <sup>+</sup> (%)	Overall	5	-1.56 (-1.80, -1.33)	<0.001	89.4
	Sensitive analysis <sup>a</sup>	5	-1.56 (-1.80, -1.33)		
	Sensitive analysis <sup>b</sup>	4	-1.69 (-1.95, -1.43)		
	Sensitive analysis <sup>c</sup>	-	-		
CD4 <sup>+</sup> (%)	Overall	5	-0.93 (-1.15, -0.72)	<0.001	88.0
	Sensitive analysis <sup>a</sup>	5	-0.93 (-1.15, -0.72)		
	Sensitive analysis <sup>b</sup>	4	-1.03 (-1.26, -0.79)		
	Sensitive analysis <sup>c</sup>	-	-		
CD8 <sup>+</sup> (%)	Overall	5	-0.04 (-0.24, 0.16)	0.706	71.2
	Sensitive analysis <sup>a</sup>	5	-0.04 (-0.24, 0.16)		
	Sensitive analysis <sup>b</sup>	4	-0.02 (-0.23, 0.20)		
	Sensitive analysis <sup>c</sup>	-	-		
CD4 <sup>+/</sup> CD8 <sup>+</sup> (%)	Overall	5	-0.54 (-0.74, -0.34)	<0.001	20.2
	Sensitive analysis <sup>a</sup>	5	-0.54 (-0.74, -0.34)		
	Sensitive analysis <sup>b</sup>	4	-0.48 (-0.70, -0.26)		
	Sensitive analysis <sup>c</sup>	-	-		

EN, enteral nutrition; PN, parenteral nutrition; N, number of samples; NA, not applicable; WMD, weighted mean difference; RR, relative risk; CI, confidence interval; ALB, albumin; PA, prealbumin; TF, transferrin; HGB, hemoglobin; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; CD3<sup>+</sup>, cluster of differentiation 3; CD4<sup>+</sup>, cluster of differentiation 4; CD8<sup>+</sup>, cluster of differentiation 8. <sup>a</sup>Sensitivity analysis was conducted by leave-one-out approach; <sup>b</sup>Sensitivity analysis was conducted by removing smallest study; <sup>c</sup>Sensitivity analysis was conducted by removing study with highest risk of bias.

**TABLE 3.** Comparing EN + PN with EN in Patients After Surgery for Gastrointestinal Cancer.

Outcomes	Indicators	N of studies	WMD/RR (95% CI)	p	$I^2$ (%)
<b>Complications</b>					
Abdominal distension	Overall	4	2.53 (1.17, 5.49)	0.019	0.0
	Sensitive analysis <sup>a</sup>	4	2.53 (1.17, 5.49)		
	Sensitive analysis <sup>b</sup>	3	2.47 (1.08, 5.63)		
	Sensitive analysis <sup>c</sup>	-	-		
Nausea/vomiting	Overall	5	2.01 (1.09, 3.71)	0.025	0.0
	Sensitive analysis <sup>a</sup>	5	2.01 (1.09, 3.71)		
	Sensitive analysis <sup>b</sup>	4	1.73 (0.86, 3.50)		
	Sensitive analysis <sup>c</sup>	4	2.72 (1.17, 6.33)		
Diarrhea	Overall	3	3.17 (1.41, 7.10)	0.005	0.0
	Sensitive analysis <sup>a</sup>	3	3.17 (1.41, 7.10)		
	Sensitive analysis <sup>b</sup>	2	3.04 (1.03, 9.03)		
	Sensitive analysis <sup>c</sup>	2	3.25 (1.13, 9.35)		
Incision infection	Overall	6	0.81 (0.45, 1.48)	0.501	0.0
	Sensitive analysis <sup>a</sup>	6	0.81 (0.45, 1.48)		
	Sensitive analysis <sup>b</sup>	5	0.73 (0.38, 1.42)		
	Sensitive analysis <sup>c</sup>	5	0.81 (0.41, 1.61)		
Anastomotic fistula	Overall	3	0.17 (0.02, 1.38)	0.097	0.0
	Sensitive analysis <sup>a</sup>	3	0.17 (0.02, 1.38)		
	Sensitive analysis <sup>b</sup>	2	0.17 (0.02, 1.38)		
	Sensitive analysis <sup>c</sup>	-	-		
<b>Postoperative recovery</b>					
Time to first flatus	Overall	6	0.80 (0.62, 0.98)	<0.001	96.1
	Sensitive analysis <sup>a</sup>	6	0.80 (0.62, 0.98)		
	Sensitive analysis <sup>b</sup>	5	0.65 (0.46, 0.85)		
	Sensitive analysis <sup>c</sup>	5	1.13 (0.92, 1.33)		
Time to first feces	Overall	4	1.86 (1.60, 2.11)	<0.001	96.6
	Sensitive analysis <sup>a</sup>	4	1.86 (1.60, 2.11)		
	Sensitive analysis <sup>b</sup>	3	1.65 (1.39, 1.92)		
	Sensitive analysis <sup>c</sup>	-	-		
Duration of hospital stay	Overall	5	0.56 (0.37, 0.75)	<0.001	91.4
	Sensitive analysis <sup>a</sup>	5	0.56 (0.37, 0.75)		
	Sensitive analysis <sup>b</sup>	4	0.49 (0.29, 0.70)		
	Sensitive analysis <sup>c</sup>	4	0.80 (0.58, 1.02)		
<b>Nutritional indicators</b>					
ALB (g/L)	Overall	6	-1.09 (-1.27, -0.91)	<0.001	93.5
	Sensitive analysis <sup>a</sup>	6	-1.09 (-1.27, -0.91)		
	Sensitive analysis <sup>b</sup>	5	-1.06 (-1.26, -0.87)		
	Sensitive analysis <sup>c</sup>	5	-1.40 (-1.61, -1.20)		

**TABLE 3.** Continued

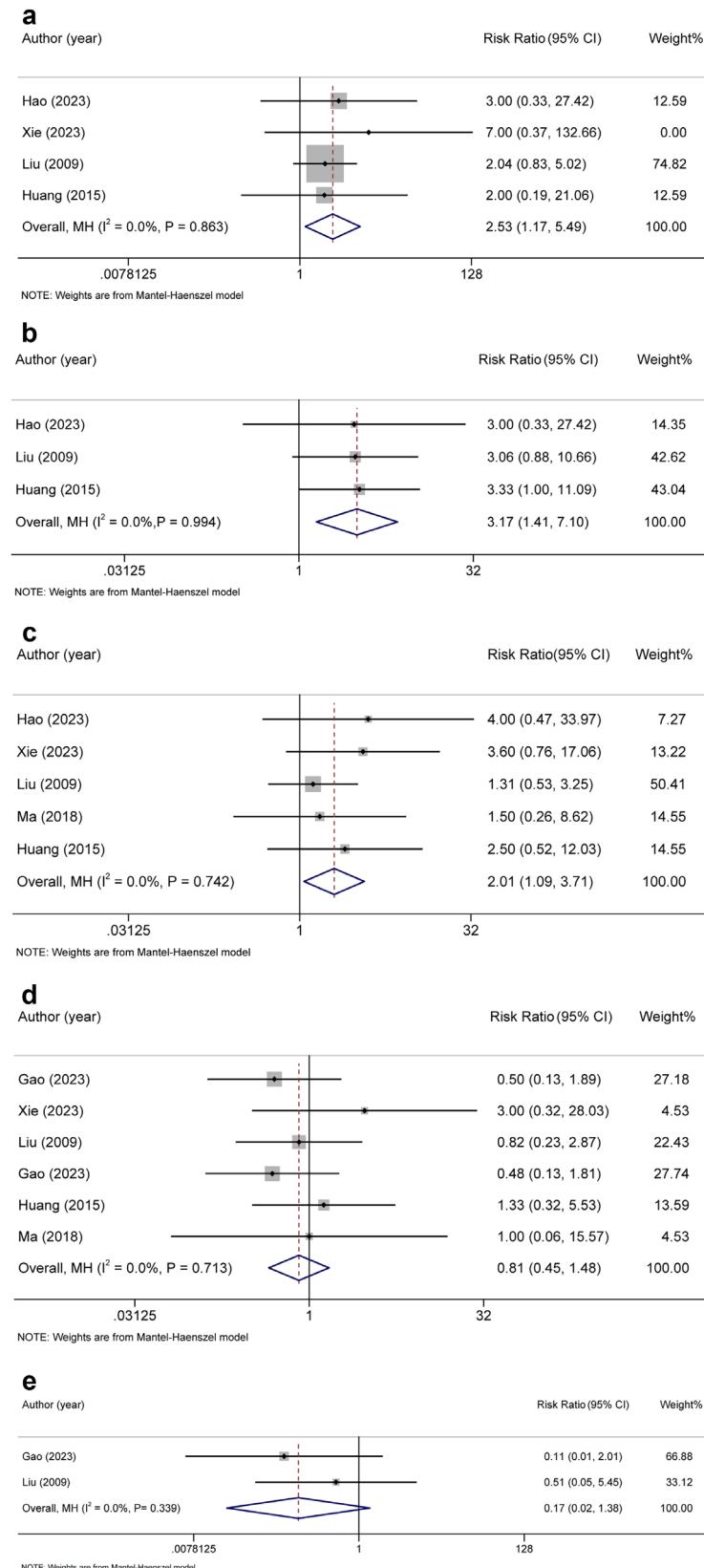
Outcomes	Indicators	N of studies	WMD/RR (95% CI)	p	I <sup>2</sup> (%)
PA (mg/L)	Overall	5	-1.20 (-1.40, -0.99)	< 0.001	90.7
	Sensitive analysis <sup>a</sup>	5	-1.20 (-1.40, -0.99)		
	Sensitive analysis <sup>b</sup>	4	-1.13 (-1.34, -0.91)		
	Sensitive analysis <sup>c</sup>	-	-		
TF (g/L)	Overall	5	-0.60 (-0.79, -0.42)	<0.001	88.4
	Sensitive analysis <sup>a</sup>	5	-0.60 (-0.79, -0.42)		
	Sensitive analysis <sup>b</sup>	4	-0.45 (-0.65, -0.25)		
	Sensitive analysis <sup>c</sup>	4	-0.67 (-0.89, -0.45)		
HGB (g/L)	Overall	2	-0.76 (-1.09, -0.44)	<0.001	96.2
	Sensitive analysis <sup>a</sup>	2	-0.76 (-1.09, -0.44)		
	Sensitive analysis <sup>b</sup>	2	-0.76 (-1.09, -0.44)		
	Sensitive analysis <sup>c</sup>	-	-		
<b>Immunological indicators</b>					
CD3 <sup>+</sup> (%)	Overall	3	-0.71 (-0.95, -0.47)	<0.001	90.7
	Sensitive analysis <sup>a</sup>	3	-0.71 (-0.95, -0.47)		
	Sensitive analysis <sup>b</sup>	2	-0.86 (-1.14, -0.58)		
	Sensitive analysis <sup>c</sup>	-	-		
CD4 <sup>+</sup> (%)	Overall	3	-0.22 (-0.45, 0.01)	0.060	31.1
	Sensitive analysis <sup>a</sup>	3	-0.22 (-0.45, 0.01)		
	Sensitive analysis <sup>b</sup>	2	-0.21 (-0.47, 0.05)		
	Sensitive analysis <sup>c</sup>	-	-		
CD4 <sup>+</sup> /CD8 <sup>+</sup> (%)	Overall	3	-0.84 (-1.08, -0.59)	<0.001	92.4
	Sensitive analysis <sup>a</sup>	3	-0.84 (-1.08, -0.59)		
	Sensitive analysis <sup>b</sup>	2	-1.06 (-1.34, -0.77)		
	Sensitive analysis <sup>c</sup>	-	-		

EN, enteral nutrition; PN, parenteral nutrition; N, number of samples; NA, not applicable; WMD, weighted mean difference; RR, relative risk; CI, confidence interval; ALB, albumin; PA, prealbumin; TF, transferrin; HGB, hemoglobin; IgA, immunoglobulin IgA; IgG, immunoglobulin G; IgM, immunoglobulin M; CD3<sup>+</sup>, cluster of differentiation 3; CD4<sup>+</sup>, cluster of differentiation 4; CD8<sup>+</sup>, cluster of differentiation 8. <sup>a</sup>Sensitivity analysis was conducted by leave-one-out approach; <sup>b</sup>Sensitivity analysis was conducted by removing smallest study; <sup>c</sup>Sensitivity analysis was conducted by removing study with highest risk of bias.

studies, the postoperative recovery, nutritional status, and immune function (CD3<sup>+</sup> level and CD4<sup>+</sup>/CD8<sup>+</sup>) were significantly better in the EN + PN group than in the EN or PN groups in our study. Previous studies have suggested that postoperative complications are lesser with EN than with PN.<sup>32,33</sup> In a comparative study of EN and PN in patients undergoing gastrectomy for gastric malignancy, Xin et al.<sup>33</sup> determined that the durations of postoperative fever and anal fatigue were longer with PN. In addition, they attributed the reduced postoperative fever duration in the EN group to a lower incidence of infection or enhanced immune system. In our study, there was no statistical difference in postoperative complications between the PN and PN + EN groups. However, the incidence of bloating, diarrhea, and vomiting was lower in the PN + EN group than in the EN group.

This may be attributed to intestinal intolerance to EN.<sup>15</sup> Although there was no difference in postoperative complications between the EN + PN and PN groups in our study, EN + PN may be a crucial postoperative nutritional support in patients with gastrointestinal cancers due to its superiority in postoperative recovery, nutritional function, and immune function.

Although EN reportedly improves gastrointestinal function, it is usually associated with a higher risk of gastrointestinal intolerance, manifesting as vomiting and reflux<sup>15,34</sup> due to postoperative intestinal injury and elevated levels of inflammatory factors.<sup>35</sup> EN provides nutrients via the gastrointestinal tract, thereby maintaining the normal function and structure of the intestinal tract.<sup>10</sup> However,



**FIG. 3.** Postoperative complication indicators in the EN and EN + PN groups: (a) abdominal distension, (b) diarrhea, (c) nausea/vomiting, (d) surgical wound infection, and (e) anastomotic fistula.

CI, confidence interval; EN, enteral nutrition, PN, parenteral nutrition.

PN provides nutrients directly via the vein, which can rapidly meet the nutritional needs of the patient.<sup>12</sup> Thus, the combined use of EN and PN can circumvent the potential deficiencies in nutrient intake that may arise from relying on a single route of supply.<sup>36</sup> The combination of EN and PN is thought to concurrently facilitate the delivery of nutrients and reduce the burden on the intestinal tract, thereby promoting the rapid recovery of intestinal function after surgery. Furthermore, EN can provide fiber and prebiotics, which promote the growth of beneficial bacteria and maintain the balance of intestinal microorganisms.<sup>37,38</sup> Specific essential nutrients, including amino acids (such as glutamine), fatty acids (such as omega-3 fatty acids), and micronutrients (such as zinc, vitamin E, and vitamin C), are vital for the immune system to function.<sup>39</sup> The PN solution usually includes lipid emulsions (LEs), complex amino acids, water-soluble vitamins, fat-soluble vitamins, glucose, electrolytes, and trace elements.<sup>40</sup> LEs are an important source of high-density energy, essential fatty acids, and fat-soluble vitamins,<sup>41</sup> while complex amino acids are crucial for tissue repair and physiological functions.<sup>42</sup> Better postoperative recovery usually results in a shorter hospital stay, whereas a slow recovery or development of complications may result in a longer hospital stay. In our study, the nutritional and immune function improved in the PN + EN group, which facilitated a better and faster postoperative recovery and shorter postoperative hospital stay. This finding highlights the critical role of postoperative nutritional support in patient recovery, and it may aid in reducing healthcare resource use and patient's financial burden.<sup>43,44</sup> When complete EN is not feasible immediately after surgery, PN can be an important source of nutrition. Subsequently, EN can be gradually introduced and eventually transitioned to the primary mode of nutritional support. This approach ensures that nutritional support is not delayed and that the gastrointestinal tract is not overburdened.

To the best of our knowledge, ours is the first meta-analysis to comprehensively evaluate the effects of postoperative EN, PN, and EN + PN in patients with gastrointestinal cancer. The study synthesized data from previous RCTs on postoperative nutritional support for gastrointestinal cancers. The study is a comprehensive comparison of two methods of nutritional support in the following four areas: postoperative recovery, nutrition, immunity, and complications. Our study results have significant clinical implications. First, the combination of EN + PN significantly facilitates patients' postoperative recovery by shortening the intestinal recovery phase and length of hospital stay. Second, the EN + PN protocol intensifies nutritional support to ensure that patients receive the necessary nutrients during the critical postoperative period, which helps to maintain or restore their physical functions. Third, the application of EN + PN strengthens the patient's immune system, which is essential to resist possible postoperative infections. Finally, by reducing the intolerance to EN, this protocol reduces the discomfort of patients, further optimizing their therapeutic experience. This study's findings present an important basis for the selection of appropriate nutritional support, allowing clinicians to consider different regimens for the personalization of treatments

to the patient's needs. With further studies, physicians will be able to optimize nutritional support strategies more precisely, thereby providing patients with more effective and safer treatment options.

Our study has certain limitations. First, the sources of heterogeneity remain unclear. Heterogeneity may be attributed to factors such as patient age, disease characteristics, nutritional status, individual differences, and the specific nutritional supplement implemented (caloric content and ratios of protein, fat, and carbohydrate may vary between EN, PN, and EN + PN). A more in-depth subgroup analysis could not be performed due to the limited data available. A meta-regression analysis may better address the heterogeneity in large datasets in future studies. Thus, more clearly standardized studies are required to benefit the analysis. Second, although an extensive database search was performed, all the included studies had been conducted in China. In the future, more multicenter studies with larger sample sizes, more diverse population, and higher treatment should be conducted. Finally, due to insufficient data on each outcome, the publication bias could not be evaluated, which might impose certain constraints on the interpretation of our findings.

In conclusion, our study provides a comprehensive evaluation of the clinical efficacy and safety of three nutritional support therapies (EN, PN, EN + PN) administered postoperatively in patients with gastrointestinal cancer. Current evidence indicates that the combined EN + PN therapy significantly improves postoperative recovery, nutritional status, immune status, and complications in patients with gastrointestinal cancer than PN or PN alone. However, due to the quality of the included studies, our findings require further validation via larger sample-sized, higher quality RCTs to establish a valid clinical basis.

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**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Authorship Contributions:** Concept- M.C., B.Y., L.D.; Design- M.C., B.Y., L.D.; Data Collection or Processing- M.C., B.Y., Y.Z.; Analysis and/or Interpretation- M.C., B.Y., Y.Z.; Writing- M.C., B.Y.; Critical Review- L.D.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

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**Supplementary Figure 1 and 2:** <https://www.balkanmedicaljournal.org/img/files/SUPPLEMENT%20FIGURE.pdf>

**Supplementary Table 1:** <https://www.balkanmedicaljournal.org/img/files/SUPPLEMENT%20TABLO.pdf>

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