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Impact of enteral immunonutrition on postoperative gastric cancer patients: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - All funding sources are supported by this unit (The first people's hoslital of Yi bin city) , the funders participate in the research, and there is no conflict of interest with the researchers.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 December 2025 and was last updated on 10 December 2025.

INTRODUCTION

Review question / Objective This systematic review and meta-analysis aims to retrieve randomized controlled trials on the application of enteral immunonutrition in gastric cancer surgery patients, comparing the effects of immunonutrition versus standard enteral nutrition on postoperative outcomes. Population: gastric cancer surgery patients; Intervention: enteral immunonutrition; Control: standard enteral nutrition; Outcomes: time to first flatus, time to first defecation, length of hospital stay, albumin, transferrin, prealbumin, IgG, IgA, CD4+, CD4+/CD8+, interleukin-6, tumor necrosis factor, procalcitonin, C-reactive protein, incidence of adverse events, and incidence of infectious complications; Study design: randomized controlled trials.

Rationale Gastric cancer, as one of the most common malignant tumors of the digestive tract, has high morbidity and mortality rates. Among its subtypes, adenocarcinoma is the most prevalent, followed by gastrointestinal stromal tumors. Surgical treatment is the primary therapeutic approach for gastric cancer. Postoperative patients often experience a state of high metabolism and catabolism, along with malabsorption issues leading to malnutrition, which is further exacerbated by surgery. Malnutrition is an independent risk factor that reduces overall survival, cancer-specific survival, and increases recurrence and metastasis rates. As a detrimental effect, it intensifies bodily stress, suppresses immune function, and disrupts inflammatory mediators. Consequently, such patients exhibit poorer nutritional status and immune function, delayed postoperative recovery, higher rates of infectious complications, and prolonged hospital stays. Studies indicate that both enteral and

parenteral nutrition can improve postoperative outcomes for gastric cancer patients. However, the choice of enteral nutrition depends on gastrointestinal tolerance. If feasible, enteral nutritional support is more aligned with the intestinal ecological environment, effectively accelerating peristalsis, improving blood circulation, maintaining intestinal mucosal barrier function, reducing plasma endotoxin levels, and preventing enterogenic infections, while also being more cost-effective than parenteral nutrition. Although standard enteral nutrition provides proteins, energy, amino acids, vitamins, and minerals, its efficacy falls short of expectations. Recent research shows that enteral immunonutrition, a novel nutritional therapy, involves supplementing standard enteral formulas with immunonutrients such as arginine, ω-3 fatty acids, glutamine, ribonucleic acids, cystine-theanine, probiotics, and dietary fiber. Compared to standard enteral nutrition, enteral immunonutrition more effectively modulates pathological changes induced by acute surgery or disease at both innate and adaptive immune levels, thereby restoring immune homeostasis and promoting patient recovery.

Condition being studied 1. Study location: Yibin City, Sichuan Province, China. Yibin First People's Hospital is a tertiary Grade A general hospital, and this is a single-center study.
2. Study period: December 7, 2025, to January 30, 2026.
3. Study background and necessity: Gastric cancer, as one of the most common malignant tumors of the digestive tract, had over 968,000 new cases and approximately 760,000 deaths globally in 2022, according to the World Cancer Research Fund (WCRF). Its incidence and mortality rates rank fourth and fifth worldwide, respectively, with higher rates in males than females and a trend toward younger onset. Among the subtypes of gastric cancer, adenocarcinoma is the most common, followed by gastrointestinal stromal tumors. Surgery remains the primary treatment for gastric cancer. Postoperative patients often experience a hypermetabolic and catabolic state, along with malabsorption issues leading to malnutrition, which is further exacerbated by surgery. Malnutrition is an independent risk factor for reduced overall survival, cancer-specific survival, and increased recurrence and metastasis rates. As a detrimental effect, it can intensify stress responses, suppress immune function, and disrupt inflammatory mediators. Consequently, these patients exhibit poorer nutritional status and immune function, delayed postoperative recovery, higher rates of infectious complications, and prolonged hospital stays. Relevant studies indicate that both enteral and parenteral nutrition can improve postoperative outcomes in gastric cancer patients. However, the choice of enteral nutrition depends on gastrointestinal tolerance. When feasible, enteral nutrition is more aligned with the intestinal microenvironment, effectively accelerating peristalsis, improving circulation, maintaining mucosal barrier function, reducing plasma endotoxin levels, and preventing enterogenic infections, while also being more cost-effective than parenteral nutrition. Although standard enteral nutrition provides proteins, energy, amino acids, vitamins, and minerals, its efficacy is suboptimal. Recent studies show that immunonutrition, a novel therapeutic approach, involves adding immunonutrients—such as arginine, ω-3 fatty acids, glutamine, nucleic acids, cystine-theanine, probiotics, and dietary fibers—to standard enteral formulas. Compared to standard enteral nutrition, immunonutrition more effectively modulates pathological changes from acute surgery or disease at both innate and adaptive immune levels, thereby restoring immune homeostasis and promoting patient recovery.

METHODS

Search strategy The systematic review strategy was developed using the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework to identify relevant randomized controlled trials (RCTs) evaluating the effects of immunoenhanced enteral nutrition on postoperative gastric cancer patients. Databases searched included CNKI, Wanfang, VIP, PubMed, Web of Science, CINAHL, and the Cochrane Library, covering studies published up to December 7, 2025. Two researchers independently screened titles and abstracts, extracted data, and assessed study quality. Meta-analysis was performed using RevMan 5.4 software, and the Cochrane Risk of Bias Tool 2.0 was used to evaluate the methodological quality of included studies.
PubMed search terms included:
MeSH terms: *Stomach and Neoplasms, Stomach Neoplasms, Gastric Cancer, Gastrointestinal Stromal Tumors, Gastrointestinal Tract, Gastric Tumors*; OR *Nutrition, Enteral Nutrition, Immunoenhanced Enteral Nutrition, Intestinal Nutrition, Immunotherapy, Standard Enteral Nutrition*; OR *Omega-3 Fatty Acids, Arginine, Ribonucleic Acid, Glutamine, Glutamates*. All potentially eligible articles were examined regardless of language or outcomes.

Inclusion criteria based on PICOS:

- **Population (P):** Postoperative gastric cancer patients.
- **Intervention (I):** Immunoenhanced enteral nutrition.
- **Comparison (C):** Enteral nutrition.
- **Outcomes (O):** First flatus, hospital stay, nutritional indicators (albumin, transferrin, prealbumin), humoral immunity (IgG, IgA), cellular immunity (CD4+, CD8+, CD4+/CD8+), adverse reaction rate, infection complication rate.
- **Study design (S):** RCTs.

Exclusion criteria:
1. Studies not examining the effects of immunoenhanced enteral nutrition vs. enteral nutrition on serum proteins, immune factors, infection complications, or cellular immune function in gastric adenocarcinoma or gastrointestinal stromal tumor patients.
2. Studies involving interventions other than immunoenhanced enteral nutrition or enteral nutrition.
3. Studies only comparing outcome measures without analyzing effects or lacking experimental data.
4. Studies with only abstracts and unavailable full texts.
5. Studies comparing immunoenhanced enteral nutrition with enteral nutrition in non-gastric cancer primary tumor patients.
6. Comprehensive studies on gastric cancer and other malignancies without separate gastric cancer patient data.

Participant or population Inclusion criteria: Participants (P): Gastric cancer surgery patients; Interventions (I): Enteral immunonutrition; Comparisons (C): Enteral nutrition; Outcomes (O): First exhaust time, hospital stay, nutritional indicators: albumin, transferrin, prealbumin; humoral immunity indicators: IgG, IgA; cellular immunity indicators: CD4+, CD8+, CD4+/CD8+, incidence of adverse reactions, incidence of infectious complications; Study design (S): Randomized controlled trial (RCT).

Exclusion criteria: (1) Literature that does not investigate the effects of enteral immunonutrition versus enteral nutrition on serum proteins, immune factors, infectious complications, and cellular immune function in gastric adenocarcinoma or gastrointestinal stromal tumor surgery patients.
(2) Literature involving interventions other than enteral immunonutrition and enteral nutrition.
(3) Literature that only compares outcome indicators without analyzing effects or lacks experimental data.
(4) Literature with only abstracts and unavailable full texts.
(5) Literature comparing the efficacy of enteral immunonutrition and enteral nutrition in patients with non-gastric primary tumors.
(6) Comprehensive studies involving gastric cancer and other malignant tumors without separately listing data for gastric cancer patients.
Research rationale:
(7) Exclude patients with unresectable tumors, those taking corticosteroids or immunosuppressants, those who have undergone abdominal radiotherapy, preoperative infections, or insufficient heart, liver, or kidney function.

Intervention Intervention: Enteral immunonutrition. Specific measures: ω-3 fatty acids + arginine, glutamine-based + enteral nutrition, ω-3 fatty acids + arginine + ribonucleic acid, etc.

Comparator Control measure: Standard enteral nutrition.

Study designs to be included Research Design: Randomized Controlled Trial (RCT).

Eligibility criteria Inclusion criteria based on PICOS:
- **Population (P):** Postoperative gastric cancer patients.
- **Intervention (I):** Immunoenhanced enteral nutrition.
- **Comparison (C):** Enteral nutrition.
- **Outcomes (O):** First flatus, hospital stay, nutritional indicators (albumin, transferrin, prealbumin), humoral immunity (IgG, IgA), cellular immunity (CD4+, CD8+, CD4+/CD8+), adverse reaction rate, infection complication rate.
- **Study design (S):** RCTs.

Exclusion criteria:
1. Studies not examining the effects of immunoenhanced enteral nutrition vs. enteral nutrition on serum proteins, immune factors, infection complications, or cellular immune function in gastric adenocarcinoma or gastrointestinal stromal tumor patients.
2. Studies involving interventions other than immunoenhanced enteral nutrition or enteral nutrition.
3. Studies only comparing outcome measures without analyzing effects or lacking experimental data.
4. Studies with only abstracts and unavailable full texts.
5. Studies comparing immunoenhanced enteral nutrition with enteral nutrition in non-gastric cancer primary tumor patients.

6. Comprehensive studies on gastric cancer and other malignancies without separate gastric cancer patient data.

Information sources The searched databases included CNKI, Wanfang, VIP, PubMed, Web of Science, CINAHL, and the Cochrane Library, as well as the Chinese Biomedical Literature Database.

Main outcome(s) Primary Outcome 1: Incidence of Infectious Complications
Definition: The proportion of patients with infectious complications (including incision infection, abdominal infection, pulmonary infection, urinary tract infection, etc.) within 7 and 30 days postoperatively.
Measurement: Based on clinical diagnostic criteria (e.g., fever, elevated white blood cell count, imaging or microbiological evidence).
Statistical method: Relative risk (RR) and 95% confidence interval (CI).
Time point: Postoperative days 7 and 30.

Primary Outcome 2: Length of Hospital Stay
Definition: The number of days from the day of surgery to the day of discharge.
Measurement: Extracted from medical records.
Statistical method: Mean difference (MD) and 95% CI.
Time point: At discharge.

Primary Outcome 3: Serum Albumin Level
Definition: Serum albumin concentration (g/L) on postoperative day 7.
Measurement: Laboratory testing.
Statistical method: Mean difference (MD) and 95% CI.
Time point: Postoperative day 7.

Additional outcome(s)
Secondary outcomes
Nutritional indicators: Transferrin, Prealbumin (postoperative day 7); Immune function indicators: IgG, IgA, CD4+, CD8+ (postoperative day 7)
Inflammatory indicators: C-reactive protein, Interleukin-6, Procalcitonin, Tumor necrosis factor (postoperative days 3 and 7)
Recovery of intestinal function: Time to first flatus, Time to first defecation (hours).

Data management
1. Data extraction form involves: dual independent extraction; cross-checking after extraction.
2. Pre-extraction training on data quality, consistency testing.
3. Storage in EXCEL or CSV format.
4. Data sharing accessibility statement and data usage policy, specifying that data is only for academic research purposes.
5. Data management tool: EndNote; Statistical analysis: RevMan 5.4.1.

Quality assessment / Risk of bias analysis Cochrane.

Strategy of data synthesis Framework for Drafting Data Integration Strategies
1. Selection of Effect Measures
Specify the types of effect measures used for each outcome:
Dichotomous variables: Relative Risk (RR), Odds Ratio (OR), or Risk Difference (RD);
Continuous variables: Mean Difference (MD) or Standardized Mean Difference (SMD);
Survival analysis: Hazard Ratio (HR).

2. Selection of Statistical Models
Heterogeneity testing methods: Q-test and I^2 statistic;
Model selection criteria: Fixed-effect model if $I^2 < 50\%$, random-effects model if $I^2 \geq 50\%$;
Pooling methods: Mantel-Haenszel method or inverse variance method.

3. Handling Heterogeneity
Exploring sources of heterogeneity: Subgroup analysis and meta-regression;
Strategies for substantial heterogeneity: Use random-effects model or conduct sensitivity analysis.

4. Assessment of Publication Bias
Funnel plot (when the number of included studies ≥ 10);
Egger's test or Begg's test.

5. Statistical Software
Specify the statistical software and version used (e.g., RevMan 5.4, Stata 17.0).

Subgroup analysis This study did not perform subgroup analysis.

Sensitivity analysis
1. Sensitivity analysis based on study quality
Exclude low-quality studies (e.g., Jadad score <3 or studies with high risk of bias in ROB assessment); perform a meta-analysis only including high-quality studies.

2. Sensitivity analysis based on sample size
Exclude small-sample studies (e.g., sample size <50); reanalyze using only large-sample studies.

3. Sensitivity analysis based on statistical model
Compare the results between fixed-effect and random-effects models; use a random-effects model when heterogeneity is high.

4. Sensitivity analysis based on publication year
Exclude early studies or include only recent studies; assess the impact of time trends on the results.

5. Excluding individual studies one by one
Remove one study at a time and re-perform the meta-analysis; evaluate the influence of each individual study on the pooled results.

Language restriction No.

Country(ies) involved China.

Keywords gastric tumor;gastriointestinal stromal tumor; gastric cancer;stomach neoplasms; enteral nutrition; immune enteral nutrition; arginine; glutamine; ribonucleic acid; Omega-3 fatty acids; standard enteral nutrition.

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Author 1 - Mao Chen - Author 1 drafted the manuscript.
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