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ORIGINAL RESEARCH

# Impact of Glutamine-Enhanced Parenteral Nutrition on Postoperative Outcomes in Colorectal Cancer Patients

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**Purpose:** This study investigated the effects of parenteral glutamine (Gln) supplement immunonutrition versus conventional nutritional support on postoperative Clavien–Dindo classification complications and recovery, perioperative nutritional status, and immune, inflammation, and safety indicators in patients with colorectal cancer (CRC).

**Patients and Methods:** Clinical data were collected for a retrospective cohort study of 178 patients (58 and 120 patients in the observation and control groups, respectively) who underwent radical resection of CRC from January 2019 to December 2021. The incidence of postoperative complications was calculated. Postoperative recovery, nutritional indicators, inflammatory factors indicator, and the safety indicators before operation and at 1, 3, and 7 days after operation were compared. SPSS 29.0 statistical software was used for statistical analysis.

**Results:** The incidence of postoperative overall complications in the control group and the observation group was 22.50% (27/120) and 17.24% (10/58), respectively, and there was no significant difference between the two groups ($P$=0.42). The incidence of postoperative complications of Clavien-Dindo grade ≥III in the control group and the observation group was 14.17% (17/120) and 3.45% (2/58), respectively, and the difference between the two groups was statistically significant ($P$=0.03). Secondary outcomes (first exhaust, defecation, and liquid diet intake times) were significantly recovered earlier in the observation group than those in the control group ($P$<0.05), while the postoperative hospital stay was significantly shorter($P$=0.04). The perioperative nutritional status did not significantly differ between the groups before and after surgery($P$>0.05), although significant differences were observed in several inflammatory and safety indicators($P$<0.05).

**Conclusion:** Unlike conventional nutritional support, postoperative parenteral Gln supplementation reduced the incidence of postoperative Clavien–Dindo complications grade ≥III in patients with CRC while increasing intestinal and immune functions, decreasing inflammation, and reducing the length of hospital stay.

**Keywords:** glutamine, parenteral nutrition, colorectal cancer, clavien–dindo complication

## Introduction

According to the 2020 Global Cancer Statistics, 560,000 new colorectal cancer (CRC) cases and 290,000 deaths were recorded in China. CRC is the second-most common cancer and the fifth-most common cause of cancer-related mortality.[1] Surgery remains the main treatment for resectable CRC,[2] but the high catabolism,[3] preoperative tension and anxiety of patients together with surgery-induced intestinal ischemia-reperfusion injury, postoperative pain, nausea and vomiting, and intestinal dysfunction often cause delayed oral intake, impairing nutrient uptake and absorption;[4,5] moreover, perioperative application of antibiotics can cause an imbalance of the intestinal flora and disruption of the intestinal barrier.[6] The prevalence of malnutrition in patients with CRC ranges from 29% to 60% and may increase during hospitalization.[7,8] Previous studies have shown that malnutrition is associated with poor clinical outcomes such as decreased immune function, increased inflammatory response, and delayed or failed wound healing. Malnutrition predicts prolonged postoperative length of hospital stay (LOS),[9] which significantly increases medical costs.[10]

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Therefore, perioperative nutritional support is crucial for patients with CRC, especially those undergoing surgical treatment.[11]

Since the 1990s, immunonutrition supported by specific nutrients, mainly glutamine (Gln), has been recognized to provide the necessary energy, improve the nutritional status of patients with cancer, and increase the number of intestinal lymphocytes, thereby regulating immune function, compared with traditional nutritional support.[12,13] Immunonutrition attenuates the increased intestinal permeability[14] and bacterial translocation[15] and regulates the inflammatory response,[16] nitrogen balance, and protein synthesis,[17] reducing the incidence of postoperative complications and shortening the LOS.[18,19] In the hypercatabolic situation of surgical stress, the requirement for Gln increases while the production capacity is impaired; consequently, the Gln obtained from dietary intake and endogenous synthesis is insufficient to meet the needs of the body,[20,21] and additional Gln supplementation is therefore required.

An aqueous solution of Gln is unstable Consequently, an alanyl-Gln (Ala-Gln) dipeptide was developed for intravenous supplementation of Gln. Ala-Gln has been used as a Gln source for total parenteral nutrition (TPN) without side effects.[22] In 1989, Ala-Gln was first applied clinically, and Stehle et al reported that Ala-Gln supplementation as TPN could maintain the Gln concentration of postoperative muscle cells in patients with CRC preoperatively and maintain the nitrogen balance.[17] In 1999, Jian et al reported that parenteral nutrition (PN) supplemented with Ala-Gln could improve the nitrogen balance, protect the intestinal barrier, and be safe for patients after major abdominal surgery.[23] Song et al reported that Gln-enriched PN improved postoperative immune function and protein metabolism in patients with CRC and enhanced the efficacy of PN.[24] In 2007, researchers reported that combined parenteral and enteral Ala-Gln supplementation during the perioperative period reduced the incidence of postoperative complications and shortened the LOS in patients with CRC.[25] Yang et al in 2021 showed that surgical site infection, anastomotic leakage, and LOS in a Gln supplementation group were significantly lower than those in the control group after radical resection of CRC.[26] This may be due to the inhibition of the production of pro-inflammatory factors TNF-α and IL-6 in the process of inflammatory response, which protects the intestinal mucosa and reduces the translocation of bacteria and toxins into the blood, thereby reducing the occurrence of postoperative complications and ultimately improving the prognosis of patients.[27]

However, clinical trials have yielded inconsistent results. A prospective, double-blind registered clinical trial by Lobo et al showed that the incidence of infectious complications in experimental and control groups was 57.4% and 44.4%, respectively, after the early use of immunomodulatory feeding containing Gln in 54 patients with upper gastrointestinal tumors after surgery, and did not find any advantage of the immunonutritional diet over enteral feeding with a standard formula.[28] Sandini et al showed that parenteral Gln supplementation reduced the LOS in patients undergoing elective major abdominal surgery but did not affect the incidence of complications.[29] In recent years, domestic and foreign guidelines and consents have become inconsistent in the application of perioperative immunonutrition; the 2019 Chinese Expert Consensus on Perioperative Nutritional Therapy for Colorectal Cancer does not recommend the routine application of immunonutrition during the perioperative period for patients with CRC.[30] The 2021 edition of the Chinese Expert Consensus on Perioperative Whole-Procedure Nutritional Management of Gastrointestinal Surgery Patients concluded that Gln supplementation is beneficial to most patients undergoing gastrointestinal surgery.[31] In 2021, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommended the application of immunonutrition in the perioperative period for gastrointestinal malignant tumors.[32] However, the mechanism by which parenteral Gln supplementation has a positive effect on CRC remains unclear.[33] Additionally, Lee et al has questioned whether the routine use of immunonutrition during the perioperative period for colon cancer is unreasonable.[34] Because they found that preoperative immunonutrition did not reduce the incidence of postoperative infectious or overall complications, nor did it reduce LOS.

Therefore, the clinical application of immunonutrition remains controversial in major guidelines and clinical trials, and further research is needed to verify the effects of immunonutrition as represented by Gln. Consequently, in this study, we reviewed the administration of Gln-enriched PN in patients with CRC to evaluate the incidence of postoperative complications, postoperative recovery, perioperative nutritional status, immune function, inflammation level, and safety indicators compared with traditional nutritional support to provide a reference for parenteral Gln supplementation in patients with CRC.

# Materials and Methods

## Materials

### Inclusion Criteria

Inclusion criteria were: (1) Age 18–85 years old, sex was not limited; (2) CRC was diagnosed by pathology and met the diagnostic criteria of the American Joint Committee on Cancer (AJCC) (8th edition, 2017) for CRC; (3) radical R0 resection of the CRC was performed; (4) no preoperative radiotherapy or other treatments for CRC were administered; (5) no use of immunosuppressants or enhancers within 6 months before surgery; (6) patients were unable to take oral food within seven days after surgery and required parenteral nutrition; or if the energy and protein provided by oral feeding combined with enteral nutrition is less than 60% of the body's target requirement, and parenteral nutrition is needed.

### Exclusion Criteria

Exclusion criteria were: (1) Presence of distant metastases; (2) complications that included organic heart disease, pulmonary infection, and other serious cardiopulmonary dysfunctions; severe liver and kidney diseases such as active hepatitis, cirrhosis, and uremia; or intestinal obstruction, intestinal perforation, intestinal bleeding, and other emergencies; and (3) presence of severe preoperative malnutrition, uncontrolled diabetes, and/or coagulation disorders. The study flow is shown in Figure 1.

### General Clinical Data

The clinical data of 178 patients with CRC who underwent radical resection of colorectal cancer in the same surgical treatment group in department of General Surgery, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, from January 2019 to December 2021 were retrospectively collected, and the general clinical data of the patients were recorded. Among them, 58 patients received Gln-enhanced parenteral nutrition support after operation and were set as the observation group. 120 cases received postoperative traditional nutritional support, which was set as control group. Data included sex, age, weight, tumor location, TNM stage, surgical method, ASA classification, surgical year, surgical time, intraoperative blood loss, intraoperative blood transfusion, preoperative nutritional status, and postoperative PN support time. This study was approved by the Ethics Committee of the Affiliated Hospital of Zunyi

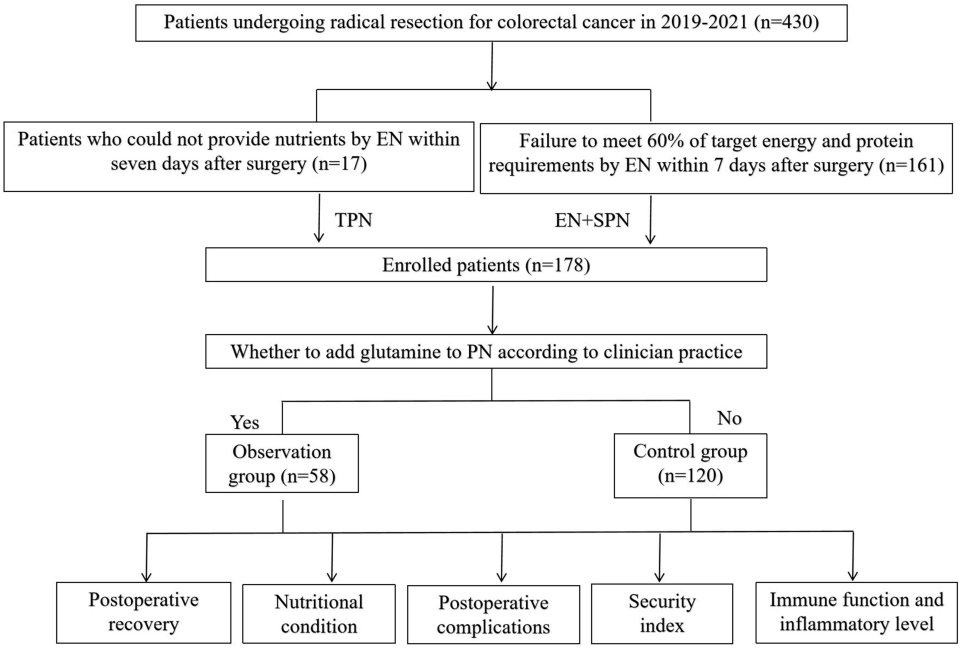


**Figure 1** Study flow chart.
**Abbreviations**: PN, Parenteral nutrition; TPN, Total parenteral nutrition; EN, Enteral nutrition; SPN, Supplemental parenteral nutrition.

Medical University (number: KLL-2023-186). Since the study was retrospective and would not adversely affect the rights and health of the subjects, the ethical committee waived the informed consent requirement. Our study complies with the Declaration of Helsinki.

## Nutritional Support

### Nutritional Support Methods Used in the Control Group

All patients diagnosed with CRC underwent surgical resection according to the tumor resection standards. Postoperative nutritional support for patients was based on the patient's body weight and postoperative intestinal recovery conditions to determine parenteral and enteral intake, and energy supply was supplied according to 25–30 kcal/(kg·d). During this period, basic treatments such as anti-infection, acid control, rehydration, and maintenance of the acid-base balance were routinely administered. PN was administered via peripheral or central venous drip at a drip rate of 50–60 drops per min and an infusion time of 10–12 h. Prescription components and dosage principles of PN nutrient solution after CRC surgery are summarized in Table 1.

### Nutritional Intervention Methods Used in the Observation Group

For nutritional support in the observation group, on the basis of the control group, a 50-mL volume of Aln-Gln injection (50 mL) was dissolved in a compound amino acid injection (250 mL) or a 100-mL volume was dissolved in a fat emulsion amino acid glucose injection (1440 mL), and the infusion time was controlled within 12–24 h through the peripheral or central vein. The duration was ≥7 days.

### Observing Indicators

#### General Indicators

Sex, age, weight, tumor location, TNM stage, surgical method, ASA, year of operation, surgical time, intraoperative blood loss, intraoperative blood transfusion, preoperative nutritional status, and postoperative PN support time.

#### Main Indicators

Postoperative complications: total complications (anastomotic leakage, anastomotic bleeding, pulmonary infection,

**Table 1** Prescription Components and Dosage Principles of PN Nutrient Solution After CRC Surgery

| PN Elements | Dosage Principle | Preparations |
|---|---|---|
| Glucose | The daily supply is maintained at 200–300 g/d, providing 50% to 70% of non-protein calories (NPC) | 5% glucose injection, 10% glucose injection |
| Amino acid | Maintain NPC (kcal): Nitrogen (g) =100 ~ 150:1 | Compound amino acid injection (18AA-V), compound amino acid injection (18AA-II), compound amino acid dipeptide injection, etc |
| Fat emulsion | To increase the proportion of fat energy supply in the diet and nutritional support formulations of cancer patients and increase the dietary energy density. The power supply accounts for 30% to 50% of the NPC. | (1)Patients with medium/long chain fat injection (20%), medium/long chain fat injection (30%), medium/long chain fat injection (C8-24), etc., (2)Hyperlipidemia (triglyceride > 3.5mmol /L) and abnormal lipid metabolism: decide whether to use fat emulsion according to the metabolic situation; (3) Patients with severe hypertriglycerides (≥5.6 mmol/L): fat emulsions were not used. |
| Micronutrients | Supplement 100% of minerals and vitamins according to the required amount, and adjust the dosage of some micronutrients according to the actual situation. | (1)Electrolyte injection: potassium chloride injection, sodium chloride injection, calcium gluconate injection, sodium potassium magnesium calcium glucose injection, invert sugar electrolyte injection, mixed sugar electrolyte injection, etc. (2) Vitamin preparations: Vitamin C, vitamin B1, vitamin B6, fat-soluble vitamin injection (I), multivitamin injection (12), a variety of trace elements injection, etc. |

abdominal infection, incision infection, etc.) and severe postoperative complications (Clavien-Dindo grade ≥III complications: surgery, endoscopy, radiological intervention, etc.; Life-threatening complications (including central nervous system complications) requiring ICU admission; Death, etc).

### Secondary Indicators

(1) Postoperative recovery: first exhaust time, first defecation time, first liquid diet time, LOS, and 30-day readmission rate. (2) Perioperative nutritional status: total protein, albumin, and prealbumin levels preoperatively and 1, 3, and 7 days postoperatively. (3) Perioperative immune function: peripheral blood lymphocyte counts preoperatively and at 1, 3, and 7 days postoperatively. (4) Perioperative inflammatory factors: white blood cell count, neutrophilic granulocyte percentage, and neutrophil/lymphocyte ratio preoperatively and at 1, 3, and 7 days postoperatively. (5) Perioperative safety indicators: alanine aminotransferase, aspartate aminotransferase, total bilirubin, endogenous creatinine clearance, and urea nitrogen levels preoperatively and 1, 3, and 7 days postoperatively.

## Statistical Methods

Statistical analyses were performed using SPSS version 29.0. The measurement data of the normal distribution were expressed as mean ± SD, and comparisons between groups were performed by an independent sample *t*-test and repeated measures ANOVA. The measurement data of the skewed distribution were expressed as M (P25, P75), and the Mann–Whitney *U*-test was used for comparison between groups. Enumeration data were expressed as percentages [n(%)], and the chi-square test or Fisher's method was used for comparison between groups. A *P*-value of <0.05 was considered significant.

# Results

## Comparison of the General Clinical Data

A total of 178 patients (121 males and 57 females) were included in the study, all of whom underwent radical resection of CRC. The age range was 22–85 years, with a mean age of 61 years. In total, 58 patients who received Gln-enhanced PN support after surgery were included in the observation group, while 120 patients received traditional nutritional support after surgery and were set as the control group. No significant differences were present in sex, age, weight, tumor location, TNM staging, surgical method, ASA, surgical year, surgical time, intraoperative blood loss, intraoperative blood transfusion, preoperative nutritional status, or postoperative PN support time between the two groups ($P$ >0.05). The results are summarized in Table 2. The PN energy supply ratio and protein energy supply of the two groups were compared, with no statistical difference ($P$>0.05). The results are shown in Table 3.

**Table 2** Comparison of General Data Between the Two Groups

| | Control group (n=120) | Observation group (n=58) | Statistical value ($t/X^2/Z$) | *P* |
|---|---|---|---|---|
| Age/year, Mean±SD | 61.27±12.17 | 61.52±11.60 | −0.13 | 0.90 |
| Gender, *n*(%) | | | 3.46 | 0.06 |
| Male | 87(72.5) | 34(58.6) | | |
| Female | 33(27.5) | 24(41.4) | | |
| Weight(kg), Mean±SD | 56.81±9.56 | 57.74±10.57 | −0.59 | 0.56 |
| Tumor location, *n*(%) | | | 0.52 | 0.47 |

(*Continued*)

**Table 2** (Continued).

| | | | | |
|---|---|---|---|---|
| Colon | 45(37.5.0) | 25(43.1) | | |
| Rectum | 75(62.5) | 33(56.9) | | |
| Stage, *n*(%) | | | 0.26 | 0.88 |
| I | 12(10.0) | 7(12.1) | | |
| II | 46(38.3) | 23(39.7) | | |
| III | 62(51.7) | 28(48.3) | | |
| Combined disease, *n*(%) | | | | |
| Hypertensive disease | 29(24.2) | 8(13.8) | 2.56 | 0.11 |
| Diabetes | 13(10.8) | 7(12.1) | 0.06 | 0.81 |
| Cardiovascular disease | 12(10.0) | 8(13.8) | 0.56 | 0.45 |
| Pulmonary disease | 18(15.0) | 10(17.2) | 0.15 | 0.70 |
| Liver and kidney disease | 11(9.2) | 11(19.0) | 3.47 | 0.06 |
| Operating method, *n*(%) | | | 2.22 | 0.30 |
| Laparoscopic | 117(97.5) | 54(93.1) | | |
| Open | 2(1.7) | 2(3.4) | | |
| Conversion | 1(0.8) | 2(3.4) | | |
| ASA, *n*(%) | | | 0.911 | 0.63 |
| 1 | 2(1.7) | 1(1.7) | | |
| 2 | 83(69.2) | 36(62.1) | | |
| 3 | 35(29.2) | 21(36.72) | | |
| Year, *n*(%) | | | 5.876 | 0.05 |
| 2019 | 40(33.3) | 10(17.2) | | |
| 2020 | 27(22.5) | 20(34.5) | | |
| 2021 | 53(44.2) | 28(48.3) | | |
| Time of operation/min, $M(P_{25}$-$P_{75})$ | 185(165–234.75) | 180 (163.75–251.25) | −0.32 | 0.75 |
| Bleeding/mL, $M(P_{25}$-$P_{75})$ | 20(10–20) | 20(13.75–20) | −0.42 | 0.67 |
| Blood transfusion | | | 0.26 | 0.61 |
| Yes | 11(9.2) | 4(6.9) | | |
| No | 109(90.8) | 54(93.1) | | |
| Postoperative PN time/day, Mean±SD | 8.68±3.23 | 9.60±3.11 | −1.79 | 0.08 |
| Nutritional status, Mean±SD | | | | |
| Total protein(g/L) | 65.55±6.37 | 66.97±5.67 | −1.44 | 0.15 |
| Albumin(g/L) | 38.89±4.16 | 39.13±4.30 | −0.36 | 0.72 |
| Prealbumin(mg/L) | 205.08±51.08 | 213.97±49.90 | −1.10 | 0.28 |

**Table 3** Comparison of the Proportion of PN Energy Supply and Protein Energy Supply Between the Two Groups

| Group | Number | PN Energy Supply Ratio (%) | | | Protein (g·kg/d) | | |
|---|---|---|---|---|---|---|---|
| | | POD 1 | POD 3 | POD 7 | POD 1 | POD 3 | POD 7 |
| Control group | 120 | 100.00±0.00 | 66.60±6.71 | 45.25±2.25 | 1.34±0.09 | 1.33±0.83 | 1.38±0.08 |
| Observation group | 58 | 100.00±0.00 | 65.76±6.67 | 46.12±1.66 | 1.37±0.09 | 1.35±0.08 | 1.37±0.10 |
| F | | 1.74 | | | 2.03 | | |
| *P* | | 0.19 | | | 0.13 | | |

**Abbreviations**: PN, Parenteral nutrition; POD, Postoperative day.

# Comparison of Main Endpoint

## Comparison of Postoperative Complications

A total of 37 patients in the two groups had postoperative complications, including 7 cases of anastomotic leakage, of which 6 cases healed after reoperation, and 1 case was improved after conservative treatment such as non-surgical drainage. Anastomotic bleeding occurred in 2 cases and healed after reoperation. 16 cases had pulmonary infection, of which 9 cases were improved after symptomatic treatment such as active anti-infection, 7 cases were transferred to ICU and improved after treatment. There were 7 cases of abdominal infection, of which 4 cases were improved after conservative treatment, and 3 cases were improved after ICU care. There were 5 cases of incision infection, of which 4 cases were improved after symptomatic treatment such as active anti-infection, and 1 case was improved after surgical treatment. In summary, the overall incidence of postoperative complications in the control group and the observation group was 22.50% (27/120) and 17.24% (10/58), respectively, and there was no significant difference between the two groups ($P$=0.42). The incidence of postoperative complications of Clavien-Dindo grade ≥III in the control group and the observation group was 14.17% (17/120) and 3.45% (2/58), respectively, and the difference between the two groups was statistically significant ($P$=0.03).The results are summarized in Tables 4 and 5.

**Table 4** Comparison of Total Complications Between Groups

| Complications | Control group (n=120) | Observation group (n=58) | $X^2$ | *P* |
|---|---|---|---|---|
| Total complications | 27 (22.50) | 10 (17.24) | 0.66 | 0.42 |
| Anastomotic leak | 5 (4.17) | 2 (3.45) | – | 1.00 |
| Anastomotic bleeding | 2 (1.67) | 0 (0.00) | – | 1.00 |
| Lung infection | 11 (9.16) | 5 (8.62) | 0.01 | 0.91 |
| Abdominal infection | 5 (4.17) | 2 (3.45) | – | 1.00 |
| Infection of incision, | 4 (3.33) | 1 (1.72) | – | 0.66 |

**Table 5** Comparison of the Incidence of Severe Postoperative Complications (Clavien-Dindo Grade ≥III) Between the Two Groups

| Complications | Control group (n=120) | Observation group (n=58) | $X^2$ | *P* |
|---|---|---|---|---|
| Severe complications | 17 (14.17) | 2 (3.45) | 4.71 | 0.03 |
| Anastomotic leak | 5 (4.17) | 1 (1.72) | – | 0.67 |
| Anastomotic bleeding | 2 (1.67) | 0 (0.00) | – | 1.00 |
| Lung infection | 6 (0.05) | 1 (1.72) | – | 0.43 |
| Abdominal infection | 3 (0.03) | 0 (0.00) | – | 0.55 |
| Infection of incision, | 1 (0.83) | 0 (0.00) | – | 1.00 |

**Table 6** Comparison of Postoperative Recovery Between the Two Groups

| Group | Number | Postoperative First Exhaust Time | Postoperative First Defecation Time | Postoperative Fluid Diet Time | Postoperative Hospital Stay | 30-day Readmis-sion Rate |
|---|---|---|---|---|---|---|
| Control group | 120 | 2.81±1.11 | 3.99±1.51 | 6.46±2.91 | 12.49±5.18 | 3 (2.50) |
| Observation group | 58 | 2.41±0.84 | 3.45±1.35 | 5.40±3.12 | 11.05±1.87 | 3 (5.17) |
| $t/X^2$ | | 2.40 | 2.33 | 2.23 | 2.05 | - |
| *P* | | 0.02 | 0.02 | 0.03 | 0.04 | 0.39 |

## Comparison of Secondary Endpoints

### Comparison of Postoperative Recovery Rates

Compared with the control group, the observation group exhibited an early recovery time of first exhaust ($P = 0.02$), time of first defecation ($P = 0.02$), time of first fluid diet ($P = 0.03$), and a shortened LOS ($P = 0.04$). No significant difference was observed in the 30-day readmission rate ($P = 0.39$) between the two groups. The results are summarized in Table 6.

### Comparison of the Perioperative Nutritional Status

No significant differences were observed in the levels of total protein ($P = 0.70$), albumin ($P = 0.80$), or prealbumin ($P = 0.10$) between the two groups on preoperative and postoperative days 1, 3, and 7. This suggests that Gln intervention does not improve the perioperative nutritional status of patients with CRC. The results are shown in Table 7.

### Comparison of the Perioperative Immune and Inflammatory Indices

Significant differences were observed in the trends in lymphocyte count ($P = 0.03$), leukocyte count ($P = 0.03$), and neutrophil percentage ($P = 0.01$) between the two groups in the preoperative period and on postoperative days 1, 3, and 7, whereas no significant difference was observed in the neutrophil/lymphocyte ratio between the two groups ($P = 0.59$). Gln supplementation has been suggested to enhance immune function and reduce postoperative inflammation. Results are represented in Table 8.

### Comparison of Perioperative Safety Indices

For liver function, significant differences were observed in alanine aminotransferase levels ($P = 0.01$) and total bilirubin levels ($P < 0.05$) on preoperative and postoperative days 1, 3, and 7 between the two groups; however, aspartate aminotransferase ($P = 0.30$) levels did not significantly differ. For renal function, significant differences were observed in the trend in urea nitrogen levels preoperatively and on postoperative days 1, 3, and 7 between the two groups ($P < 0.05$) but not in the endogenous creatinine clearance rate ($P = 0.79$). These results suggest that the Gln application impairs liver and kidney function. Results are represented in Tables 9 and 10.

## Discussion

Gln is the most abundant free amino acid in the human body and plays important roles in intermediary metabolism, ammonia-nitrogen transport between tissues, and pH homeostasis.[35] Gln is an essential nutrient for lymphocyte proliferation and cytokine production, phagocytosis and secretion by macrophages, and the bactericidal activity of neutrophils.[36] The release and utilization of Gln in circulation are mainly controlled by key metabolic organs, such as the gut, liver, and skeletal muscle. During high levels of catabolism, Gln is essential for metabolic function, but its availability is mostly limited because of the impaired homeostasis of amino acid metabolism between tissues.[37] Initially, Gln supplementation was mostly used in critically ill or surgical patients. In a meta-analysis of 40 randomized controlled trials involving 3107 critically ill or postoperative patients, Bollhalder et al reported that parenteral Gln supplementation significantly reduced the incidence of infectious complications and LOS; a trend toward lower short-term mortality was observed, but this difference was not significant.[38] In recent years, the incidence of malnutrition among oncology patients

**Table 7** Comparison of Perioperative Nutritional Status Indexes Between the Two Groups

| Group | Number | Total Protein(g/L) | | | | Albumin(g/L) | | | | Prealbumin(mg/L) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Preoperative | POD 1 | POD 3 | POD 7 | Preoperative | POD 1 | POD 3 | POD 7 | Preoperative | POD 1 | POD 3 | POD 7 |
| Control group | 120 | 65.55 ±6.37 | 56.72 ±4.99 | 59.78 ±5.48 | 61.92 ±7.28 | 38.89 ±4.16 | 32.83 ±3.59 | 33.74 ±3.74 | 35.48 ±4.93 | 205.08 ±51.08 | 152.94 ±45.71 | 148.05 ±50.28 | 181.11 ±60.49 |
| Observation group | 58 | 66.97 ±5.67 | 57.10 ±6.56 | 59.86 ±6.39 | 62.20 ±7.29 | 39.13 ±4.30 | 32.67 ±4.80 | 33.18 ±3.55 | 35.30 ±4.43 | 213.97 ±49.90 | 160.02 ±47.21 | 139.50 ±45.95 | 181.28 ±57.15 |
| F | | 0.47 | | | | 0.33 | | | | 2.10 | | | |
| *P* | | 0.70 | | | | 0.80 | | | | 0.10 | | | |

**Abbreviation**: POD, Postoperative day.



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**Table 8** Comparison of Perioperative Immune and Inflammatory Indexes Between the Two Groups

| Group | Number | Lymphocyte Count (×10⁹/L) | | | | White Blood Cell Count (×10⁹/L) | | | | Neutrophilic Granulocyte Percentage | | | | Neutrophil/Lymphocyte Ratio | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Preoperative | POD 1 | POD 3 | POD 7 | Preoperative | POD 1 | POD 3 | POD 7 | Preoperative | POD 1 | POD 3 | POD 7 | Preoperative | POD 1 | POD 3 | POD 7 |
| Control group | 120 | 1.54±0.61 | 0.86 ±0.42 | 0.97 ±0.41 | 1.17 ±0.58 | 5.73±1.70 | 10.54 ±4.71 | 6.87 ±2.38 | 6.10 ±2.47 | 0.61±0.11 | 0.84 ±0.66 | 0.74 ±0.09 | 0.67 ±0.12 | 2.67±1.99 | 12.54 ±7.52 | 6.41 ±4.42 | 4.82 ±5.85 |
| Observation group | 58 | 1.72 ±0.59 | 0.87 ±0.39 | 0.97 ±0.36 | 1.36 ±0.69 | 6.53±2.03 | 11.71 ±3.44 | 6.85 ±1.97 | 5.91 ±1.68 | 0.61.±0.85 | 0.85 ±0.54 | 0.75 ±0.09 | 0.62 ±0.09 | 2.51±1.22 | 13.74 ±7.80 | 6.99 ±4.75 | 4.71 ±6.58 |
| F | | 3.00 | | | | 3.07 | | | | 3.74 | | | | 0.64 | | | |
| *P* | | 0.03 | | | | 0.03 | | | | 0.01 | | | | 0.59 | | | |

**Abbreviation**: POD, Postoperative day.

**Table 9** Comparison of Perioperative Liver Function Between the Two Groups

| Group | Number | Alanine Aminotransferase(U/L) | | | | Aspartate Transaminase(U/L) | | | | Total Bilirubin(μmol/L) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Preoperative | POD 1 | POD 3 | POD 7 | Preoperative | POD 1 | POD 3 | POD 7 | Preoperative | POD 1 | POD 3 | POD 7 |
| Control group | 120 | 20.41 ±17.34 | 14.72 ±8.99 | 15.72 ±11.90 | 21.73 ±16.75 | 27.13 ±16.73 | 24.69 ±9.87 | 24.2 ±12.22 | 27.29 ±14.13 | 11.53 ±5.01 | 16.07 ±9.81 | 13.21 ±6.79 | 12.17 ±6.49 |
| Observation group | 58 | 15.79 ±10.11 | 12.34 ±5.41 | 18.84 ±14.75 | 25.84 ±24.10 | 23.59 ±10.54 | 22.71 ±7.86 | 27.98 ±15.81 | 27.62 ±14.01 | 11.65 ±6.55 | 14.86 ±8.86 | 17.95 ±11.98 | 15.41 ±13.93 |
| F | | 3.87 | | | | 3.06 | | | | 6.45 | | | |
| *P* | | 0.01 | | | | 0.30 | | | | <0.05 | | | |

**Abbreviation**: POD, Postoperative day.



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**Table 10** Comparison of Perioperative Renal Function Between the Two Groups

| Group | Number | Urea Nitrogen(mmol/L) | | | | Endogenous Creatinine Clearance Rate(μmol/L) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Preoperative | POD 1 | POD 3 | POD 7 | Preoperative | POD 1 | POD 3 | POD 7 |
| Control group | 120 | 5.02±1.71 | 3.59 ±1.76 | 4.35 ±1.99 | 4.60 ±2.16 | 76.57±17.66 | 75.49 ±18.25 | 68.63 ±17.61 | 69.74 ±17.58 |
| Observation group | 58 | 5.45±1.54 | 4.32 ±2.19 | 6.34 ±2.66 | 6.38 ±2.27 | 78.38±28.83 | 77.55 ±24.58 | 70.76 ±25.09 | 70.33 ±20.52 |
| F | | 7.82 | | | | 0.36 | | | |
| *P* | | <0.05 | | | | 0.79 | | | |

**Abbreviation**: POD, Postoperative day.

has been increasing annually, and approximately 30–80% of oncology patients are at risk of malnutrition,[39] which is an independent risk factor for complications after gastrointestinal surgery.[40] Therefore, Gln is now included in clinical nutritional supplementation programs.

To explore the effect of Gln application on postoperative complications in patients with CRCs, many previous studies have used total infectious complications, and noninfectious complications as observational indicators. A retrospective study in 2021 included 1004 CRC surgical patients (of whom 660 received intravenous Gln supplementation) and reported that the postoperative total complication incidence in the Gln and control groups was 14.9% and 36.8%, respectively, and that the incidence of postoperative infectious complications was significantly lower in the Gln group than that in the control group (10.5% versus 28.9%).[41] A retrospective study by Wei et al reported that Gln-enhanced PN reduced the incidence of complications in older adult patients with CRC (7.50% versus 17.50%, P <0.05), accelerated perioperative recovery, and improved patient prognosis.[42] In recent years, the Clavien–Dindo classification has been used as an observation index of postoperative complications in clinical practice for improved assessment and management of postoperative complications.[43] Therefore, our current retrospective study investigated the effect of postoperative Gln on the severity of postoperative complications by observing whether this had been provided parenterally to patients with CRC after surgery. The results showed that parenteral Gln supplementation reduced the incidence of postoperative complications of Clavien-Dindo grade ≥III, which confirmed the effectiveness of Gln in patients with CRC. Previous studies showed that Gln supplementation reduced the incidence of postoperative infectious and non-infectious complications, and found its effect on improving the severity of postoperative complications. Our study also found that parenteral Gln supplementation had a tendency to reduce postoperative complications such as anastomotic leakage, bleeding and postoperative infection, but the difference did not reach statistical significance, which may be due to the small number of subjects included in the study, and further study with larger sample should be continued.

For postoperative recovery, our study observed that the time to first flatus ($P = 0.02$), first defecation ($P = 0.02$), first liquid diet ($P = 0.03$), and LOS ($P = 0.04$) in the observation group were earlier than those in the control group, suggesting that Gln improved gastrointestinal function, which is consistent with results of previous studies. In 2019, Chaidez et al reported that intravenous infusion of Gln after gastrointestinal tumor surgery changed the assessment of gastrointestinal function from severe to mild dysfunction in the supplemented group ($P = 0.0001$) and that the non-supplemented group progressed from moderate to severe dysfunction, suggesting that supplementation of Gln by PN can improve gastrointestinal function.[44] Gln can activate the mammalian target of rapamycin, increase the expression of ornithine decarboxylase, and promote intestinal repair.[45] Gln can upregulate the expression of antiapoptotic proteins Bcl-2 and CD45RO and downregulate that of proapoptotic proteins Fas and Fas ligands in the human T lymphocyte Jurkat cell line.[46] In this study, no significant difference was observed in the 30-day readmission rates ($P = 0.39$) between the groups. We believe that the maintenance time in this study was mainly 7–10 days, which is a short-term application of immunonutrition therapy, and may have had minimal effect on relatively long-term observation indicators.

Gln oxidation can provide a nitrogen source for protein synthesis.[47] Our study showed that the preoperative nutritional status did not differ between the two groups, with no significant difference in the change trends of total

protein, albumin, and prealbumin levels on postoperative days 1, 3, and 7 between the groups ($P$ >0.05), suggesting that Gln intervention did not improve the nutritional status of patients in the short term. This is inconsistent with the results of recent studies. Kai Xiong et al reported that nutritional status indicators (albumin, prealbumin, and nitrogen balance) were significantly improved after Gln treatment in patients with CRC undergoing radical resection.[48] Gang Tang et al enrolled 1004 patients with CRC undergoing elective surgery and reported that Gln supplementation attenuated the decline in albumin ($P$ <0.001), total protein ($P$ <0.001), and prealbumin levels ($P$ <0.001).[49] The decrease in serum protein levels after CRC surgery is affected by many factors, one of which may be the increase in capillary permeability caused by the inflammatory effect of surgical stimulation, causing the leakage of plasma proteins through capillaries.[50] The half-life of albumin is approximately 21 days, and the short-term monitoring of nutritional status within 7 days after surgery in our study may not reflect the true plasma level. Our findings suggest that postoperative Gln supplementation enhances immune function and reduces postoperative inflammation to an extent. This is consistent with previous studies, and an earlier clinical trial reported that Gln caused an increase in total lymphocyte count, CD8+, CD4+, IgA, and IgG levels, and a decrease in C-reactive protein levels in immunocompromised patients.[51] The mechanism whereby Gln exerts an anti-inflammatory effect may be via the inhibition of various inflammatory response pathways such as NF-kB, p38MAPK, ERK, and MKP-1; Gln has an inhibitory effect on the increase in iNOS expression.[16] In addition, Gln plays a role in controlling cell proliferation in the immune system by activating proteins such as ERK and JNK,[36] maintaining Paneth and goblet cell numbers, normalizing Th2 cytokines, and increasing resistance to bacterial mucosal invasion.[52] Finally, in terms of safety indicators, we defined the clearance rate of transaminase, total bilirubin, urea nitrogen and creatinine. Glutamine is usually metabolized by the liver, and it is necessary to dynamically monitor the liver and kidney function of CRC patients when glutamine preparation is applied in clinical. Our study showed that the application of Gln after surgery in CRC patients can damage liver function to a certain extent while increasing the nitrogen levels in the body, but this statistical difference has no clinical significance.

Our study has several advantages. First, by comparing the effects of general nutritional support and Gln-enriched PN on the clinical outcomes of patients with CRC, the advantages of Gln were verified to provide a clinical basis for perioperative nutritional support programs for patients with CRC. Second, this study classified the main endpoints as grade I–II and ≥III concurrently according to the Clavien–Dindo classification, which is more in line with clinical practice and better reflects the improvement of postoperative complications in patients with CRC. Third, We reviewed studies in other fields and found that for patients with liver cancer, pancreatic cancer et al during the perioperative period, glutamine supplementation also had a positive effect on reducing the incidence of postoperative complications, shortening LOS, and ultimately improving the prognosis of patients.[53,54] Therefore, we believe that the study population and the findings can be generalized to other types of surgeries or patient demographics. This study had a limitation, this is a single-center retrospective study, which inevitably has some confounding factors or selection bias. In order to minimize the influence of these factors or bias, we formulated and implemented strict inclusion and exclusion criteria, and the patients were precisely set as the control and the observation group according to the different nutritional support methods in the past. And our team is considering to conduct a follow-up prospective randomized controlled study on related topics to improve the reliability of the conclusion.

## Conclusion

Compared with traditional nutritional support therapy, postoperative PN with glutamine supplementation can reduce the incidence of Clavien-Dindo≥III complications in patients with CRC, promote the recovery of intestinal function, shorten LOS, improve immune function, and reduce inflammation to a certain extent. This is closely related to the function of glutamine to protect the intestinal barrier and reduce the translocation of bacteria and toxins into the blood. Due to the limitations of a retrospective study, we could not control variables in advance to completely eliminate the confounding factors of this study, so future implementation of a multicenter prospective study is warranted. Secondly, the universality of glutamine in other settings should also be explored, and the positive effects of its application in patients with other tumors or surgery should be explored to bring the greatest benefits to hospitalized patients and give full play to the advantages of glutamine as an immunonutrient. Finally, the specific mechanism of action, application time, optimal dose of glutamine, and the efficacy of adjuvant therapy such as radiotherapy and chemotherapy are the focus of future research.

## Data Sharing Statement

The first author is available to provide data and materials upon request.(Yong Huang, Email:2227830103@qq.com).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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