

Original Article

The effects of early enteral nutrition on the nutritional statuses, gastrointestinal functions, and inflammatory responses of gastrointestinal tumor patients

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Abstract: Objective: This paper was designed to investigate the effects of early enteral nutrition (EEN) on the nutritional statuses, gastrointestinal functions, and inflammatory responses of gastrointestinal tumor patients. Methods: A total of 194 gastrointestinal tumor patients treated in our hospital from May 2017 to February 2019 were recruited as the study cohort. Among them, 101 patients were administered enteral nutrition (the study group), and 93 patients were administered parenteral nutrition (the control group). The two groups were compared in terms of their nutritional statuses, gastrointestinal functions, inflammatory responses, and other indicators. Results: On the third day after the operation (postoperative 3 d), the serum albumin (ALB) and prealbumin (PA) levels were significantly reduced in both groups ($P>0.05$). On the seventh day after the operation (postoperative 7 d), the two nutritional indices increased significantly in both groups ($P<0.05$), and were significantly higher in the study group ($P<0.05$). Compared with the control group, the patients in the study group experienced shorter lengths of stay (LOS), earlier first anal exhaust times, and faster intestinal peristalsis recovery times ($P<0.05$). On the third day after the operations, the high-sensitive C-reactive protein (hs-CRP) and prostaglandin E (PGE) levels were significantly reduced in both groups ($P<0.05$), and the decrease was significantly greater in the study group ($P<0.05$). In addition, the CD3⁺, CD4⁺, CD8⁺ and CD4⁺/CD8⁺ levels were significantly reduced in both groups on the third day after the operation ($P>0.05$). On the seventh day after the operation, the first three immune indices increased significantly in both groups ($P<0.05$), and they were significantly higher in the study group ($P<0.05$). The incidences of vomiting, diarrhea, and abdominal distension in the study group were significantly lower than they were in the control group ($P<0.05$). After the treatment, the patients' quality of life (QOL) was significantly higher in the study group ($P<0.05$). Conclusion: For gastrointestinal tumor patients, EEN can improve their gastrointestinal functions, enhance their immune functions, and reduce their expressions of inflammatory cytokines while improving their nutritional statuses and QOL.

Keywords: Early enteral nutrition, gastrointestinal tumor, nutritional status, gastrointestinal functions, inflammatory responses

Introduction

As one of the most common malignant tumors, gastrointestinal tumors have brought a heavy burden to individual health and the social economy [1]. The disease has an increasing mortality rate and incidence, and its pathogenic sites include the esophagus, stomach, biliary tree, pancreas, small intestine, large intestine, rec-

tum, and anus [2]. Gastrointestinal cancer remains one of the major causes of cancer-related deaths [3], accounting for 38% of human cancers and 45% of deaths according to some studies [4]. The causes of gastrointestinal tumors are closely related to lifestyle, environment, and abnormal heredity [5]. Clinically, patients with the disease have poor chemotherapy tolerance, long infection and hospital-

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ization times, and low overall survival rates [6, 7]. The accepted and standard treatment methods for the disease are surgical resection and perioperative adjunctive therapies, which result in inevitable changes in body composition, such as weight loss and skeletal muscle loss during the treatment [8]. Moreover, due to the tumor locations and other reasons, about 60% of patients also suffer from malnutrition to varying degrees [9]. Therefore, it is necessary to study the nutritional statuses and the gastrointestinal function recoveries of gastrointestinal tumor patients.

As minimally-invasive and low-risk therapeutic method, enteral nutrition support provides patients with high-energy and nutritious artificial nutritional supplements in the form of a powder or liquid, usually connecting to the gastrointestinal tract through catheters or stomas [10]. It helps to provide short-term or long-term nutrition for patients whose gastrointestinal tracts cannot maintain adequate nutritional needs for a long time [11]. As suggested by the *2016 Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient In 2016* from the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN), enteral nutrition support should be started as early as possible within 48 hours for critically ill patients who cannot take enough oral nutrition [12]. There are studies showing that this method is also beneficial to non-critically ill patients [13].

In this study, after the treatments, the nutritional statuses, the gastrointestinal functions, and inflammatory responses of the gastrointestinal tumor patients were compared between the two groups that were treated with different types of nutritional support, in order to discuss the influences of the different nutritional support treatments on the patients.

Materials and methods

General information

A total of 194 gastrointestinal tumor patients who were treated in Eastern Hospital of Yangzhou University were recruited as the study cohort. Among them, 101 patients (56 males and 45 females) with an average age of

(53.87±10.42) years old who were administered enteral nutrition were enrolled in the study group. Also, 93 patients (51 males and 42 females) with an average age of (52.94±11.17) years old who were administered parenteral nutrition were placed in the control group. Inclusion criteria: Patients who were accompanied by their family members on admission, patients who had complete pathological data, and patients who were confirmed to have a gastrointestinal tumor through pathological examinations and who then underwent surgery. Exclusion criteria: Patients with a history of mental illness or a family history of psychosis, patients with a history of autoimmune deficiencies, severe organ diseases or drug dependence, and patients who could not cooperate with the examinations due to communication disorders that were caused by aphasia, dysphoria or unconsciousness. This study was approved by the Ethics Committee of our hospital. The patients and their families signed the informed consent forms after learning about the experimental processes.

Methods

The patients in the control group were administered parenteral nutrition support, with a post-operative support energy of 25-35 kcal/kg daily. The enteral nutrition support was given to them after their gastrointestinal functions recovered. The patients in the study group were administered early enteral nutrition (EEN) and postoperative routine fluid replacement. The nutrient canal was indwelt through the nose, and its end was located in the upper jejunum. Isotonic glucose (500 mL) was given at 20-35 mL/h on the 1st day after each operation, and the enteral nutrition preparations (1000-2500 mL/d) were given on the 2nd-8th days after each operation. The patients' tolerance was observed, and the amounts and speeds of the infusions were adjusted based on each patient's tolerance. If they suffered from intolerance symptoms such as abdominal distension, nausea, or vomiting, the speed was reduced. In severe cases, the infusion was stopped, and an alternative treatment was administered. The total energy support was maintained at 25-35 kcal/kg daily, and part of the energy could be supplemented through parenteral pathways at the same time.

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Table 1. Comparison of the general patient data ($\bar{x} \pm s$)/[n (%)]

	Study group (n=101)	Control group (n=93)	t/ χ^2	P
Age (years)	53.87±10.42	52.94±11.17	0.60	0.55
Body mass index (kg/m ²)	21.35±4.24	20.89±5.61	0.65	0.52
Gender			0.01	0.93
Male	56 (55.45)	51 (54.84)		
Female	45 (44.55)	42 (45.16)		
Intraoperative blood loss (mL)	181.26±67.54	183.17±68.27	0.20	0.85
Operative time (h)	3.12±0.56	3.09±0.44	0.41	0.68
Tumor stages			0.01	0.91
I-II	47 (46.53)	44 (47.31)		
III-IV	54 (53.47)	49 (52.69)		
Tumor sites				
Gastric cancer	31 (30.69)	28 (30.11)	0.01	0.93
Colorectal cancer	64 (63.37)	60 (64.52)	0.03	0.87
Others	6 (5.94)	5 (5.37)	0.03	0.87

Outcome measures

After the patients fasted for 12 hours, their venous blood was collected in the morning before the operation (preoperative), on the third day after the operation (postoperative 3 d) and on the seventh day after the operation (postoperative 7 d), respectively. The nutritional indices such as serum albumin (ALB) and prealbumin (PA) were measured using blood biochemical examinations. The immune indexes of the lymphocyte subsets CD3⁺, CD4⁺, CD8⁺ and CD4⁺/CD8⁺ were measured using flow cytometry (FCM) in both groups. Five ml of peripheral venous blood was isolated from the external blood using a separating medium (Yuanmu Biotechnology Co., Ltd., Shanghai, YS6132), and the cell concentration was adjusted to 1×10⁶/L after washing the blood three times with PBS (LMAI Bio, Shanghai, LM0221A). The above samples (100 µl) were placed in 4 tubes and incubated in the dark for 25 min at room temperature. Then, the FCM (Image Trading Co., Ltd., Beijing) was used to make the determinations. The optical path of the instrument was calibrated with fluorescent microspheres CS&T and 7-color to make the resolution work optimally. The cells were obtained and analyzed using Cell Quest software to create and analyze the CD3⁺, CD4⁺, CD8⁺ scatter plots before and after the treatment, and the CD4⁺/CD8⁺ levels were calculated. On the 3rd day after each operation and the nutritional support, the patients' peripheral

venous blood was collected, in which the inflammatory mediators such as high-sensitive C-reactive protein (hs-CRP) and prostaglandin E (PGE) were measured using enzyme-linked immunosorbent assays. The lengths of stay (LOS), the first anal exhaust times, the intestinal peristalsis recovery times, and the occurrence of adverse reactions (vomiting, diarrhea, abdominal distension) in both groups were recorded. The MOS 36-item Short-Form Health Survey (SF-36) [14] was used to evaluate the patients' quality of life

(QOL) from the four aspects of emotion, spirit, physiology, and society. Higher scores indicate better QOL.

Statistical methods

In this study, the statistical analysis of all experimental results was conducted using SPSS 20.0 (IBM Corp, Armonk, NY, USA). GraphPad Prism 7 (GraphPad Software, Inc., San Diego CA, USA) was used to plot the figures. The count data were expressed as [n (%)], and the comparison between groups were conducted using chi-square tests. The measurement data were expressed as ($\bar{x} \pm s$), and the comparisons between two groups were conducted using t tests. When P<0.05, the difference was considered statistically significant.

Results

Comparison of general information

The general information, such as age, gender, and tumor sites, was collected from the study group and the control group, as shown in **Table 1**. There was no significant difference in the general information between the two groups (P>0.05).

Comparison of LOS

We recorded the LOS in the two groups after the treatment, which was significantly lower in the study group than it was in the control group

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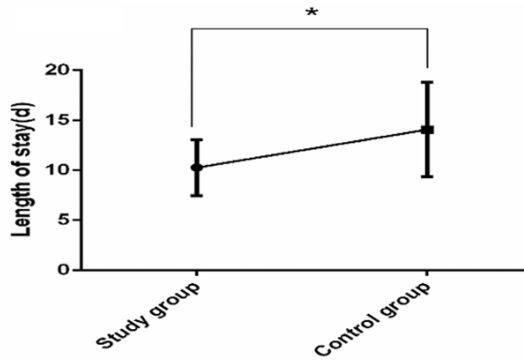


Figure 1. Comparison of LOS. After the treatment, the LOS in the study group was significantly shorter than it was in the control group. Note: * indicates $P < 0.05$ when there is a comparison between two groups.

after the treatment ($P < 0.05$), as shown in **Figure 1**.

Comparison of the nutritional indices

The nutritional indices were also compared between the two groups of patients, as shown in **Figure 2**. Before the operations, there were no significant differences in the two indices in the two groups ($P > 0.05$). On the third day after the operations, the indices were significantly lower in both groups ($P > 0.05$), but they were not significantly different between the two groups. On the seventh day after the operations, the indices were significantly higher in both groups ($P < 0.05$), and they were significantly higher in the study group ($P < 0.05$).

Comparison of the gastrointestinal function recovery

The gastrointestinal function recovery was compared between the two groups, as shown in **Figure 3**. Compared with the control group, the study group had earlier first anal exhaust times, faster intestinal peristalsis recovery times, and better gastrointestinal function recovery ($P < 0.05$).

Comparison of the inflammatory mediator levels

The inflammatory mediator levels (hs-CRP and PGE) were compared between the two groups, as shown in **Figure 4**. Immediately after the operations (postoperative immediately), there were no significant differences in the two medi-

ators in the two groups ($P > 0.05$). On the third day after the operations, the mediators were significantly lower in both groups ($P < 0.05$), and the decrease was significantly greater in the study group ($P < 0.05$), indicating significantly better levels of the postoperative inflammatory mediators in the study group.

Comparison of the immune indices

The immune indices ($CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$) were compared between the two groups, as shown in **Figure 5**. Before the operation, the four indices were not significantly different between the two groups ($P > 0.05$). On the third day after the operation, the indices were significantly lower in both groups ($P > 0.05$), but there was no significant difference between the two groups. On the seventh day after the operations, the first three indices in both groups increased significantly ($P < 0.05$), and they were significantly higher in the study group ($P < 0.05$).

Comparison of the incidence of adverse reactions

The occurrence of adverse reactions during the treatment was compared between the two groups, as shown in **Table 2**. In this study, the different intolerance levels in the patients were relieved after the corresponding treatments. The incidences of vomiting, diarrhea and abdominal distension were significantly lower in the study group ($P < 0.05$).

Comparison of the QOL after the treatment

The patients' QOL was compared between the two groups, as shown in **Figure 6**. After the treatment, the emotional, spiritual, physiological, and social scores in the study group were all significantly higher than the corresponding scores in the control group ($P < 0.05$), indicating that EEN can effectively improve the QOL of gastrointestinal tumor patients.

Discussion

Gastrointestinal tumors are the most common malignant tumor among the Chinese people. According to China's tumor registry and monitoring data, gastric cancer ranks second, and its cases account for 12.67% of all cases of malignant tumors. Colorectal cancer ranks third, and its cases account for 10.30%. In

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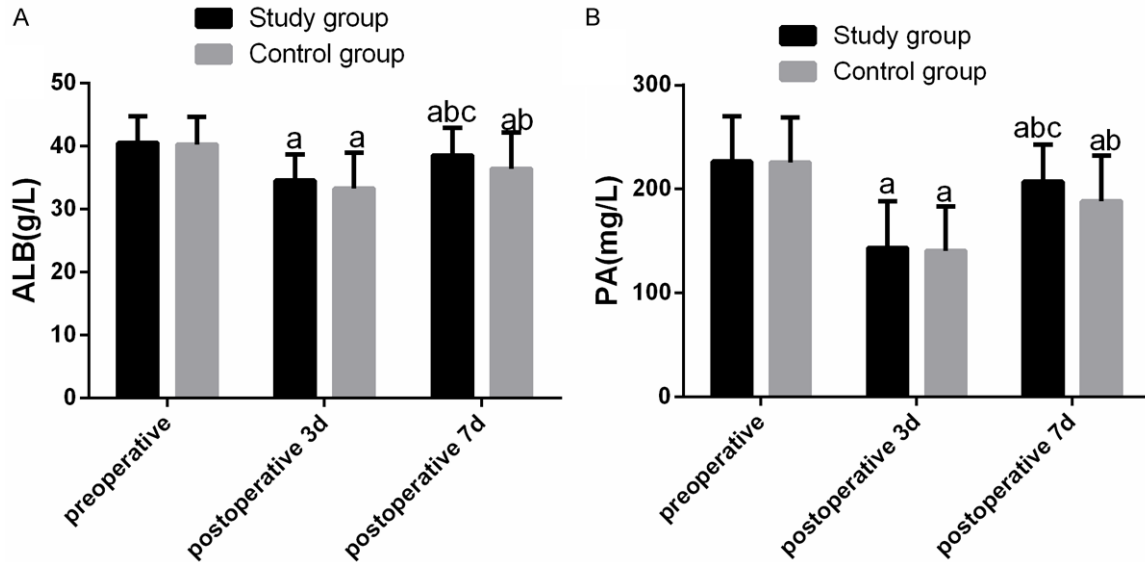


Figure 2. Comparison of the nutritional indices. A: Before the operations, the serum ALB levels were not significantly different between the two groups. On the third day after operation, this index decreased significantly in both groups. On the seventh day after the operation, it increased significantly in both groups, and was significantly higher in the study group. B: Before the operations, the serum PA levels were not significantly different between the two groups. On the third day after the operations, the serum PA levels were significantly lower in both groups. On the seventh day after the operation, the levels increased significantly in both groups, and were significantly higher in the study group. Note: a indicates $P < 0.05$ compared with before the operation. b indicates $P < 0.05$ compared with the third day after the operation. c indicates $P < 0.05$ compared with the seventh day after the operation.

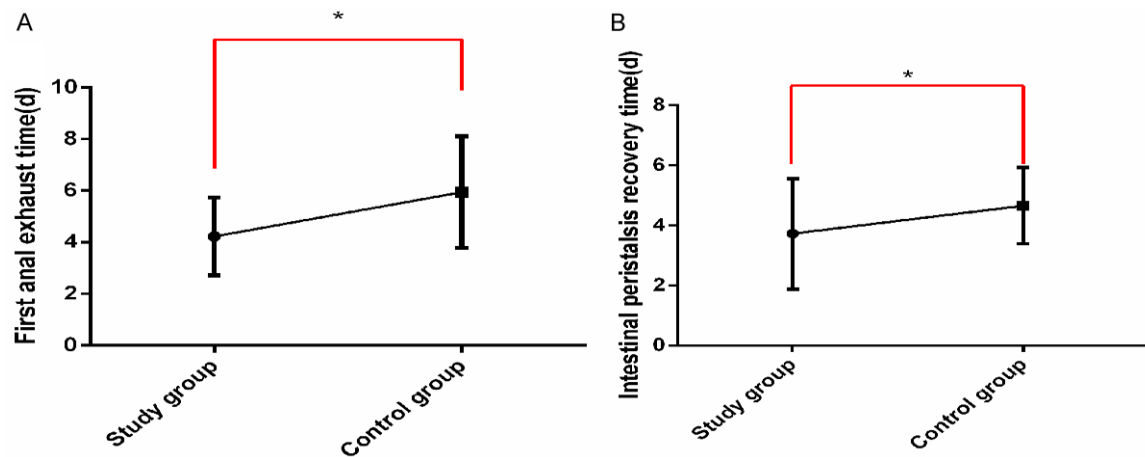


Figure 3. Comparison of the gastrointestinal function recovery. A: The first anal exhaust times in the study group were earlier than they were in the control group. B: The intestinal peristalsis recovery time in the study group is shorter than it was in the control group. Note: * indicates $P < 0.05$ when there is a comparison between two groups.

addition, there are about 122,100 elderly patients diagnosed with gastric cancer over 75 years old in China every year, accounting for 42.73% of the global cases of the same age. There are about 78,200 elderly patients with colorectal cancer, accounting for 18.08% of the global cases [15]. The annual hospitalization

rate of gastrointestinal diseases has also increased from 47.13/100,000 to 52.41/100,000 [16]. According to previous studies, 50-90% of patients with malignant tumors develop weight loss and are at a high risk for malnutrition, especially those with head and neck cancers and malignant gastrointestinal

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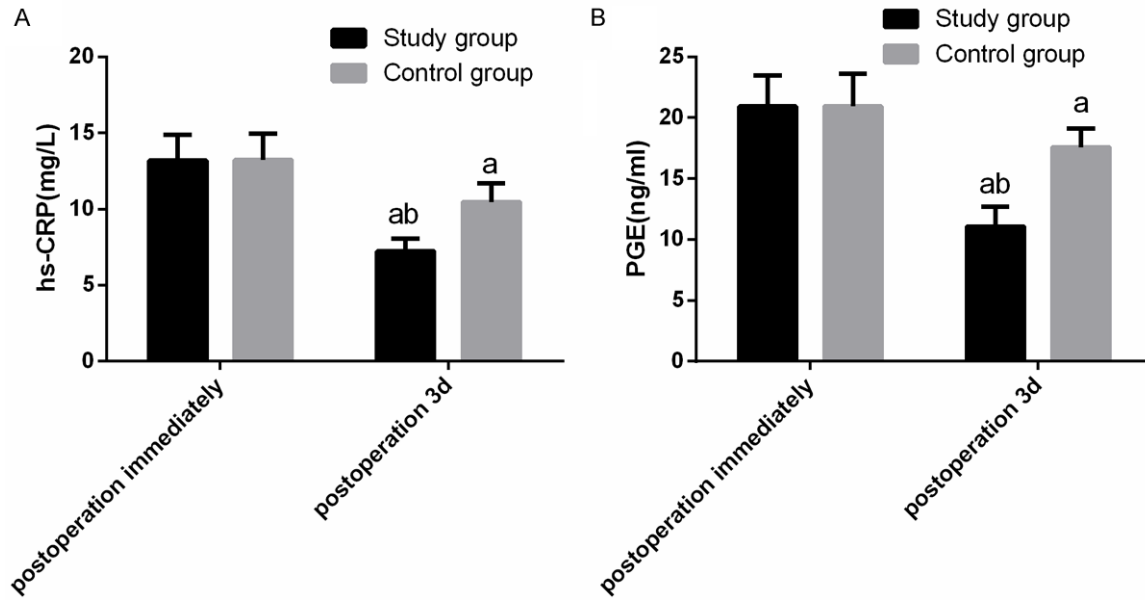


Figure 4. Comparison of inflammatory mediator levels. A: Immediately after the operations, the hs-CRP levels were not significantly different between the two groups. On the third day after operations, this mediator in both groups was significantly lower, and the decrease was significantly greater in the study group. B: Immediately after the operation, the PGE was not significantly different between the two groups. On the third day after the operations, this mediator in both groups was significantly lower, and the decrease was significantly greater in the study group. Note: a indicates $P < 0.05$ compared with the same group immediately after operation. b indicates $P < 0.05$ compared with the control group on the 3rd day after operation.

tumors. Approximately 20% of patients die of malnutrition and related complications, not from the malignant tumors themselves [17]. Due to the tumor sites, pathophysiology, and other characteristics, gastrointestinal tumors aggravate malnutrition [18], which therefore is extremely common in patients with gastrointestinal system tumors [19]. Some studies have shown that the nutritional statuses of patients with gastrointestinal cancer are also closely related to their prognoses [20], so it is necessary to evaluate their nutritional statuses.

In this study, on the third day after being administered the nutritional support, the serum ALB and PA were reduced significantly in both groups, but they increased significantly on the seventh day after the operation. This suggests that both nutritional support treatments can effectively improve patients' nutritional statuses. On the seventh day after the operation, the two indices were significantly higher in the study group, indicating that EEN can improve the nutritional statuses of the patients more effectively. This is consistent with the findings that enteral nutrition support can improve the postoperative nutritional status of patients

with gastric cancer and promote their rehabilitation [21].

Inflammatory responses play an important role in the development and progression of diseases, and systemic inflammation has a great effect on the development of cancer cachexia, which can induce the progressive loss of body weight and muscle mass and is usually the major cause of cancers and patient deaths [22]. Enteral nutrition support therapy can improve patients' nutritional statuses and regulate their inflammation during the perioperative period [23]. Therefore, in this study, the inflammatory mediator levels were compared between the two groups. On the third day after being administered nutritional support, the hs-CRP and PGE levels in the two groups were reduced significantly, and the decrease was significantly greater in the study group. This indicates that both nutritional support treatments can reduce the expressions of inflammatory cytokines in patients, but EEN is more effective. In addition, the inflammatory markers in patients with gastrointestinal cancer are significantly related to their malnutrition; that is to say, higher inflammatory responses reflect a

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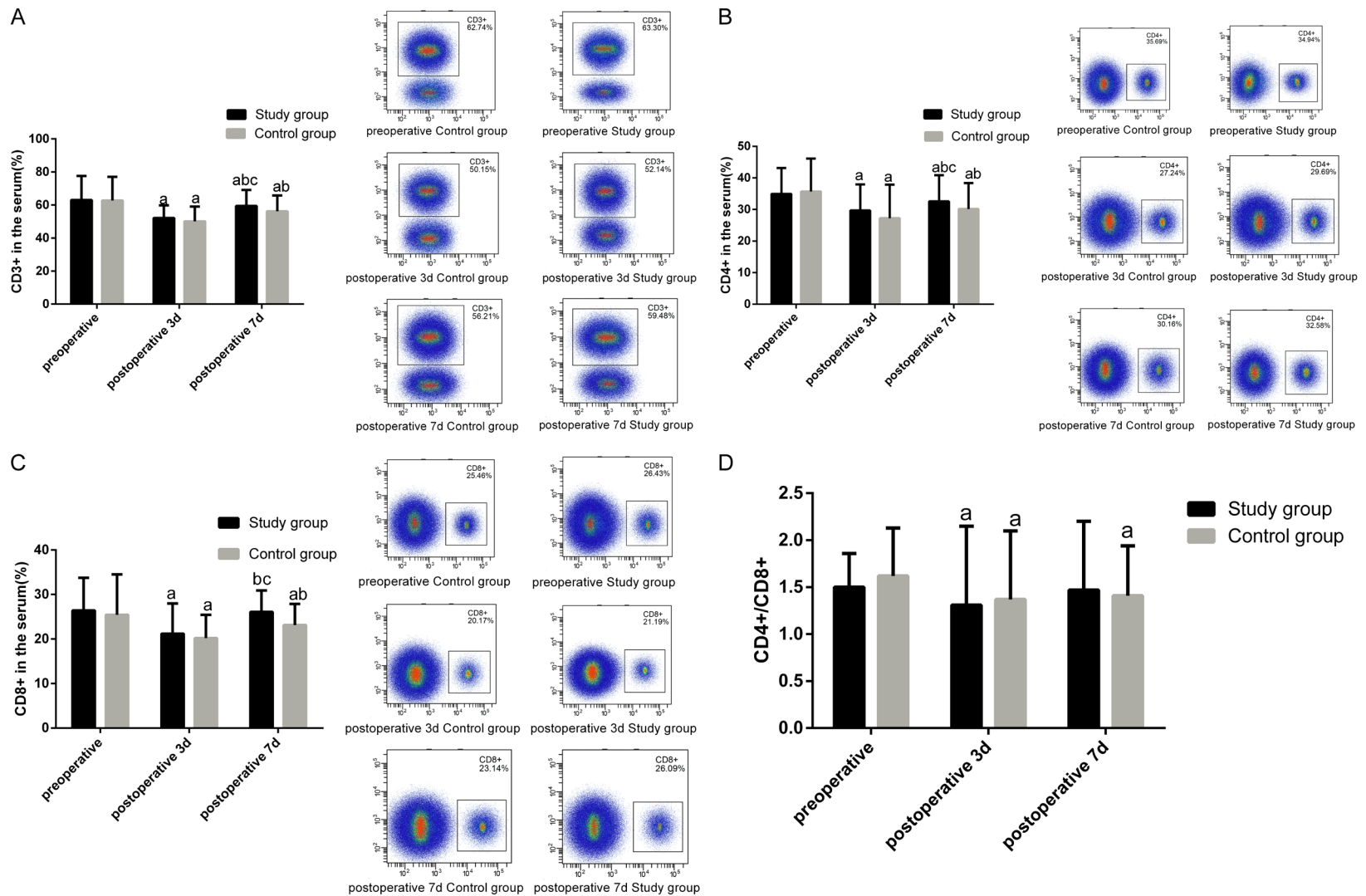


Figure 5. Comparison of the immune indices. A: A comparison of the CD3⁺ levels between the two groups. B: A comparison of the CD4⁺ levels between the two groups. C: A comparison of the CD8⁺ levels between the two groups. D: A comparison of the CD4⁺/CD8⁺ levels between the two groups. Note: a indicates P<0.05 compared with before the operation. b indicates P<0.05 compared with the third day after the operation. c indicates P<0.05 compared with the seventh day after the operation.

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Table 2. The incidences of adverse reactions during the treatment [n (%)]

	Vomiting	Diarrhea	Abdominal distention
Study group (n=101)	5 (4.95)	6 (5.94)	29 (28.71)
Control group (n=93)	14 (15.03)	15 (16.13)	42 (45.16)
X ²	5.59	5.21	5.65
P	0.02	0.02	0.02

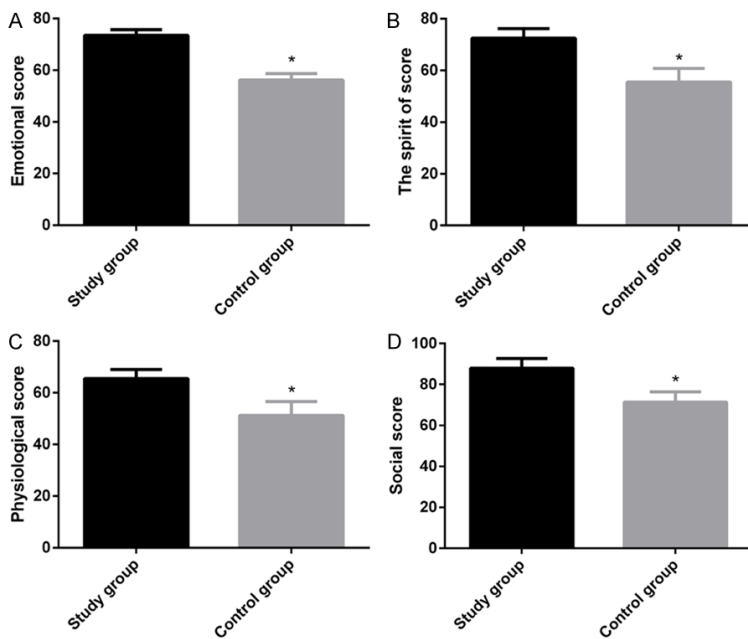


Figure 6. Comparison of the SF-36 scores. A: The emotional scores in the study group are significantly higher than the corresponding scores in the control group. B: The spiritual scores in the study group are significantly higher than the corresponding scores in the control group. C: The physiological scores in the study group are significantly higher than the corresponding scores in the control group. D: The social scores in the study group are significantly higher than the corresponding scores in the control group. Note: * indicates $P < 0.05$ when there is a comparison between two groups.

worse nutritional status [24]. This is basically consistent with the results of this study. In this study, the nutritional statuses and the expressions of the inflammatory cytokines were better in the study group.

Previous studies reported that malnutrition is correlated with prolonged LOS [25], but others have concluded that the LOS in the EEN group was significantly shorter than it was in the parenteral nutrition group [26]. This is consistent with the findings of this study, namely that the LOA was significantly shorter in the study group. Enteral nutrition support can be the first feeding method if clinically permitted, because it nourishes the intestinal tract and stimulates

the recovery of intestinal functions [27]. This is consistent with the findings of this study that the study group had earlier first anal exhaust times and faster intestinal peristalsis recovery times. This indicates that enteral nutrition support can effectively improve the gastrointestinal functions of gastrointestinal tumor patients.

The patients' immune functions will decrease after the operations, but both enteral and parenteral nutrition can improve the patients' nutritional statuses and enhance their immune functions [26]. In this study, on the third day after the operation, the CD3⁺, CD4⁺, CD8⁺ and CD4⁺/CD8⁺ levels in both groups were reduced significantly. On the 7th day after operation, the first three immune indices were significantly higher in both groups, and they were significantly higher in the study group. This suggests that EEN can enhance the immune functions of the body and promote the immune function recovery of T lymphocytes more effectively. According to previous studies, nutritional treatment can promote the wound healing of critically ill patients, and re-

duce the incidence of complications [28]. In terms of adverse reactions, compared with enteral nutrition support, patients treated with parenteral nutrition have higher incidences of sepsis, catheter-related bloodstream infections, thrombosis, and hepatic dysfunction [27, 29, 30], which is consistent with the findings of this study that the incidence of adverse reactions is significantly lower in the study group. The QOL of well-nourished patients is different from the QOL of malnourished patients. With the progression of diseases, patients have relatively poor overall prognosis when their QOL is severely impaired [31]. In this study, after the treatment, the QOL of the patients was significantly higher in the study group in the four

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aspects of emotion, spirit, physiology, and society, indicating that EEN can effectively improve the QOL of gastrointestinal tumor patients.

This study has comprehensively discussed the effects of two nutritional support treatments on patients with gastrointestinal tumors. However, there are still some shortcomings because of the many factors that affect the recovery of the patients. Therefore, the influences of different doses on patient recovery in different environments should be specifically analyzed, in order to provide a basis for treating the disease better in the future.

In summary, for gastrointestinal tumor patients, EEN can improve the gastrointestinal functions, enhance their immune functions, and reduce their expressions of inflammatory cytokines while improving their nutritional status and QOL.

Disclosure of conflict of interest

None.

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