

Advances in Enteral Nutrition for Short- and Long-Term Prognosis in Post-PLC Surgery Patients

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Abstract: Primary liver cancer (PLC) is one of the most frequent hepatic malignancies in China, characterized by its significant incidence and mortality rates. The prevalence of malnutrition among patients with PLC after surgery is also high, which raises the risk of mortality and complications and negatively influences the overall assessment of the effectiveness of the therapy and prognosis. Physiological compatibility, maintenance of the intestinal barrier function, and regulation of immune responses make enteral nutrition (EN) a commonly used nutritional support method in the postoperative period following PLC surgery. The article is a systematic review of the short- and long-term consequences of EN in postoperative PLC patients. As has been shown by existing evidence, early short-term EN can speed up the recovery of gastrointestinal function, significantly enhance postoperative liver function indicators (ALT, AST, and ALB), raise CD3⁺ and CD4⁺ T cell counts, and decrease the amount of inflammatory cytokines, including TNF α and IL-6. Nutritional status is significantly associated with long-term survival in PLC patients, and EN appears to have the potential benefits in enhancing quality of life and long-term survival.

Keywords: Enteral nutrition; Primary liver cancer; Liver function; Immune function; Nutritional status

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1. Introduction

Primary liver cancer (PLC) is usually used to refer to a malignant tumor that arises in hepatocytes and intrahepatic bile duct epithelial cells, which are primarily hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined hepatocellular-cholangiocarcinoma (cHCC-CCA). It is the most prevalent hepatic malignancy in China. Typical symptoms are dull pain in the liver area, systemic digestive symptoms, progressive increase in liver size, and jaundice.

PLC is now one of the major issues of public health in China due to socioeconomic progress along

with better living conditions, and both the incidence and mortality rates are some of the highest among all cancers. The available information indicates that there were around 865,000 new cases of PLC globally in 2022, with around 367,700 of them in China, which was the 6th most widespread type of cancer globally, with 758,000 people dying of the disease, including 316,500 (the 3rd leading cause of cancer death) in China. PLC incidence and deaths were dominated by HCC globally, 79.2 percent and 78.8 percent, respectively. HCC incidence and deaths in mainland China represented 45.2 percent and 44.6 percent of the overall global figures, respectively ^[1]. Surgical resection, transarterial chemoembolization (TACE), radiotherapy, and other methods are frequently applied in clinical practice to extend patient life. Nevertheless, there is growing evidence that most postoperative PLC patients have chronic poor nutritional status. This can be elucidated in several aspects: first, as a consumptive disease, PLC causes stress responses after surgical trauma, which subsequently increases the load on different organ systems and worsens the hypermetabolic state; second, postoperative hepatic dysfunction directly interferes with the digestive and absorptive processes of nutrients, causing absorptive dysfunction and hence resulting in either the onset of or progression to prolonged malnutrition; moreover, postoperative patients might develop anorexia and lethargy for psychological reasons, which makes it challenging to satisfy energy demands with a normal diet. These possible postoperative elements not only make the chances of mortality and complications more evident but also negatively impact the overall assessment of treatment efficacy and long-term prognosis ^[2].

The existing nutritional care system in China is currently developing, and many hospitals have not set up official certification and standardization processes for clinical nutrition services. Currently, the percentage of tertiary-grade A hospitals with nutrition departments in China is quite small, and the volume of patients undergoing clinical nutrition intervention is limited. The amount of attention given to the issue of malnutrition by society and the healthcare system is also much lower compared to that on the international level. Also, there is an unequal distribution of nutritional medical resources across regions, cooperation between disciplines has not been developed, and collaboration in clinical practice and research in this sphere needs more thoroughness and perfection ^[3].

During the last few years, due to ongoing research development and growing consciousness among people about nutrition, enteral nutrition has become quite noticeable. Enteral nutrition (EN) is one of the medical support strategies that supply nutrients to the gastrointestinal tract through oral, nasogastric tube, or gastrostomy/jejunostomy tube pathways. In comparison with parenteral nutrition support, EN has such benefits as the direct absorption and use of nutrients by the intestine (more similar to the natural pattern of metabolism of endogenous nutrients), the convenience of administration, low cost, and preservation of intestinal functional integrity and prevention of intestinal mucosal atrophy. EN, as a new treatment, is beneficial to postoperative recovery, quality of life, and prognosis of PLC patients, and is effective in satisfying nutritional requirements, enhancing nutritional condition, sustaining metabolic equilibrium, and minimizing complications.

The existing literature is largely comprised of clinical experimental research and largely concentrates on gastrointestinal or other digestive system tumors or other systemic diseases. It has also not been systematically reviewed and analyzed how nutritional status relates to EN in postoperative PLC patients. Hence, the purpose of this paper is to review the development of research in EN to enhance the short-and-long-term outcomes of postoperative PLC patients, and to summarize the underlying mechanisms and effects that would serve as a reference and guide to the postoperative rehabilitation and prognosis of PLC patients.

2. Shortterm effects of enteral nutrition on postoperative PLC patients

2.1. Acceleration of gastrointestinal function recovery

Gastrointestinal paralysis following surgery is one of the frequent complications after hepatectomy in PLC patients and is characterized by reduced bowel movements, slow return of flatus and defecation, and so on. Not only does it inhibit nutrient absorption, but it can also increase endotoxin translocation and systemic inflammatory reactions, and thus represents a significant barrier to early recovery. Enteral feeding is often delayed until the return of gastrointestinal activity and discharge of flatus. Nevertheless, enteral nutrition may be introduced as early as 24 hours after the surgery and through direct stimulation of the intestinal mucosa and enhancement of gut peristalsis, it has an important role in increasing short-term nutrient uptake. One study that involved 108 HCC patients was prospective controlled study demonstrating that the group of patients who received enteral nutrition had significantly less time to recover of bowel sounds (9.83 h vs. 11.48 h, $P < 0.001$), first flatus (20.27 h vs. 25.98 h, $P < 0.001$), and first defecation (55.97 h vs. 63.92 h, $P < 0.001$) than the control group that underwent routine care without enteral nutrition ^[4] suggesting that enteral nutrition can be effective in alleviating postoperative ileus.

2.2. Improvement of liver function and nutritional status

The hypercatabolic state is commonly observed in postoperative PLC patients because it is related to surgical trauma, stress reactions, and inadequate hepatic reserve that predispose them to hypoalbuminemia and negative nitrogen balance. However, postoperative catabolism also aggravates the state of the liver, resulting in chronic malnutrition. Available evidence suggests that enteral nutrition is associated with improved liver performance and nutritional condition, postoperative immune regeneration, and reduced recovery period in postoperative PLC patients. In an experiment ($n = 150$) testing the effectiveness of laparoscopic hepatectomy and early enteral intravenous nutrition support in PLC, it was determined that the intervention of enteral nutrition within 24 hours after surgery significantly reduced the levels of AST and ALT through the nasogastric tube, whereas the level of TBIL increased significantly (all $P < 0.05$) ^[5]. A different study ($n = 62$) to determine whether enteral nutrition affected liver functionality and inflammatory reactions in patients with hepatic dysfunction following abdominal surgery demonstrated that after six days of enteral nutrition intervention, the number of patients who had abnormal γ -glutamyl transferase decreased from 40 to 30 ($P = 0.041$); the number who had abnormal preoperative total bilirubin decreased from 9 to 3 ($P = 0.034$); and the values of ALT (29.26 U/L vs. 35.46 U/L, $P = 0.228$), AST (27.97 U/L vs. 33.59 U/L, $P = 0.155$), and AKP (98.87 U/L vs. 103.86 U/L, $P = 0.821$) were all better than preoperative values ^[6].

The enhancement in liver functioning through enteral nutrition can be explained by the fact that it provides the substrates necessary to repair hepatocytes (amino acids) and also sufficient energetic support that indirectly enhances the recovery of hepatic functions. The results of a prospective trial ($n = 98$) demonstrated that after enteral nutrition intervention, the values of TRF (2.87 g/L vs. 2.41 g/L), PA (16.76 mg/dl vs. 14.87 mg/dl), and ALB (39.87 g/L vs. 35.85 g/L) of the study group were significantly higher than those before the intervention ($P < 0.05$) ^[7]. Furthermore, the nutrients delivered by enteral nutrition directly enter the blood through the small intestine, causing the intestinal neuroendocrine system to produce and release gastrointestinal hormones, which are then returned to the portal vein via the mesenteric veins, raising blood flow to the liver and other parts of the body and protecting the hepatic system ^[6] and alleviating the effects of hypoxemia and hypoalbuminemia.

2.3. Regulation of immune function

Patients treated with postoperative PLC are frequently immunosuppressed, due to surgical trauma, blood loss, and immune paralysis associated with their underlying liver disease. Enteral nutrition has the potential to regulate systemic immunity through the preservation of the intestinal mucosal barrier and decreased endotoxin crossing over. Within the last few years, numerous high-quality studies have validated the immunomodulatory properties of enteral nutrition in postoperative PLC patients. Retrospective study data ($n = 80$) revealed significantly higher levels of immune parameters ($CD4^+$: 31.9 vs. 28.3, $P < 0.01$; $CD8^+$: 30.5 vs. 27.7, $P < 0.01$) and lower levels of inflammatory cytokines (IL-1: 50.3 pg/mL vs. 61.6 pg/mL, $P < 0.01$; IL-6: 97.7 pg/mL vs. 155.4 pg/mL, $P < 0.01$; TNF α : 53.2 pg/mL vs. 65.0 pg/mL) in the enteral nutrition group compared to the control group^[8]. Another meta-analysis of randomized controlled trials ($n = 705$) published in 2022 also found that serum endotoxin concentration and inflammatory cytokine levels (TNF- α and IL-6) were decreased after enteral eco-immunonutrition (EEIN) in patients who underwent hepatectomy; the concentrations of immunoglobulin A (g/L) (MD 0.24; 95% CI, 0.14 -0.35; $P < 0.00001$), immunoglobulin G (g/L) (MD 1.52; 95% CI, 1.22 -1.82; $P < 0.00001$), and immunoglobulin M (g/L) were all raised relative to the control group^[9]. The mechanism behind this phenomenon is intimately linked to the supply of immunomodulatory substrates like glutamine and arginine through enteral nutrition, which restores the intestinal mucosal barrier (as shown by lower D-lactate and I-FABP), thus limiting the continued activation of the immune system by bacterial endotoxins. The effective reconstitution of the immune system is highly important in decreasing postoperative infections and overall recovery^[10].

3. Longterm effects of enteral nutrition on postoperative PLC patients

In comparison to short-term effectiveness, the role played by enteral nutrition in the long-term prognostic effect of postoperative PLC patients is also a subject of concern. The available research has been primarily concerned with two aspects, namely, long-term survival and quality of life.

Deprivation of nutrients may lead to decreased capacity for repair in the body, poor prognosis, and low quality of life among patients, but enteral nutrition is an effective way to manage postoperative malnutrition. Research results of a retrospective study ($n = 293$) showed that severely malnourished individuals had much shorter median overall survival (43 months compared to 129 months) and recurrence-free survival (20 months compared to 54 months) than those who were not malnourished^[11]. This means that the nutritional needs of postoperative patients should be met, nutritional status improved, and metabolic balance maintained to ensure long-term survival, and enteral nutrition should not be disregarded^[12].

The assessment of the quality of life is an essential endpoint to determine the total effectiveness of the therapeutic process after PLC surgery, as it represents the recovery of patients in various aspects such as physical, psychological, and social functioning. Various studies have verified the beneficial impact of early enteral nutrition on the quality of life of surgery patients. In a prospective RCT ($n = 98$), pre-operative and post-operative scores of a short-form health survey (8 dimensions and 36 items, with each item scored between 0 and 100, and higher scores indicating a better quality of life) were measured before and after enteral nutrition intervention, and after intervention, the study group scored significantly higher than the control group in terms of general health (78.93 vs. 63.18), bodily pain (79.18 vs. 63.32), physical functioning (80.81 vs. 63.45), role-physical (82.17 vs. 65.87), vitality (79.83 vs. 61.29), social functioning (80.38 vs.

62.08), role-emotional (78.19 vs. 62.16), and mental health (81.76 vs. 63.29) ^[7]. This may be due to the introduction of standardized nutritional care protocols following enteral nutrition intervention, whereby patients can actively engage in the nutritional support plan, hence a feeling of involvement at all stages of rehabilitation and prognosis, and boost patients' confidence in postoperative recovery ^[7]. A 2025 research based on the FACT-Hep (version 4) scale in elderly PLC patients (n = 120) also verified that the early EN group was significantly superior in all the quality-of-life domains (physical well-being, social/family well-being, emotional well-being, functional well-being, and hepatobiliary-specific domain) and overall score (76.25 vs. 87.89) compared to the conventional diet group when discharged ($P < 0.05$), and Cox multivariate regression indicated that early postoperative EN was a standalone protective factor in 1-year survival (95% CI 0.144-0.793; $P < 0.05$) ^[13]. The mechanism could possibly be linked to the improvement of nutritional status by EN, the enhancement of liver function recovery, and anti-inflammatory effects. Enhancement of nutritional status has a direct positive effect on the physical strength and activity of the patient; restoring liver function reduces the influence of ascites, jaundice, and other symptoms on the daily routine; restoration of immune function can decrease the adverse impact of infections and other complications on the quality of life. Early enteral nutrition, due to its multi-target action, has positive effects in enhancing the quality of life of postoperative PLC patients ^[5].

4. Types of enteral nutrition formulations and selection of nutritional support strategies for postoperative PLC patients

The current formulations of enteral nutrition that are clinically available to postoperative PLC patients can be divided into three major groups, namely: amino acid-based, short-peptide-based, and whole-protein-based formulations. Various kinds also vary by dosage, pathway of nutrient absorption, and impact on the maintenance of the intestinal mucosal barrier, which has a direct influence on the recovery of PLC patients after surgery and their prognosis ^[14]. Clinically, personalized regimens need to be chosen depending on the patient's gastrointestinal status after surgery to enhance recovery and prognosis.

Existing research suggests that supplying proper enteral nutrition formulations to postoperative PLC patients at various stages may result in the optimization of clinical outcomes and enhancement of postoperative nutritional status. Theoretically, the most appropriate formulation is based on amino acids, which contain free amino acids as the main source of nitrogen and can be absorbed directly by the intestinal mucosa without digestion, and so would be best used in patients in the initial postoperative period where gastrointestinal function has not yet been restored. In a controlled study of 207 postoperative patients with hepatocellular carcinoma with cirrhosis, the amino acid-based formulation group had a shorter time to flatus than the whole-protein-based formulation group [(55.87 vs. 68.27 h), $P = 0.0001$], and there were no significant differences between the two groups in the occurrence of abdominal distension (10.58% versus 13.59%, $P = 0.506$), postoperative hospitalization (10.30 days versus 10.12 days, $P = 0.738$), or complication rate (43.27% versus 33.98%, $P = 0.170$), although the frequency of diarrhea was higher in the amino acid-based group (23.08% vs. 8.74%, $P = 0.005$) ^[15]. The results suggest that amino acid-based formulations are better in terms of intestinal functional recovery and protein synthesis, but are less tolerated by the intestine than whole-protein-based formulations.

The formulations based on whole proteins are relatively inexpensive; however, they require that the digestive and absorptive functions be intact and are likely to cause abdominal distension and feeding

intolerance in the initial postoperative stage. The formulations containing hydrolyzed protein as the primary nitrogen source are appropriate to use in patients with impaired digestive function. Due to these differences, sequential early enteral nutrition has slowly taken center stage in China, where a transition is made in steps between the amino acid-based formulations, the short-peptide-based formulations, and finally the whole-protein-based formulations, as a way of restoring gastrointestinal function gradually and providing a comfortable recovery phase postoperatively. Simultaneously, postoperative infections are prevented by introducing immune-boosting formulations containing pharmacological nutrients like glutamine and arginine to address the diverse infective symptoms that could arise after surgery. Better clarification of the indications and evidence-based basis of various enteral nutrition formulations may help in fulfilling the personalized nutritional needs of postoperative PLC patients and provide the basis for later assessment of overall therapeutic effectiveness ^[14].

5. Conclusion

The problem of frequent postoperative malnutrition in patients with primary liver cancer has turned into a possible factor that negatively influences further prognostic assessment and rehabilitation. Due to its physiological compatibility, the maintenance of intestinal integrity, and its ability to influence immunity, enteral nutrition has been suggested in several guidelines as the most beneficial type of nutrition after surgery. The present paper is a systematic review of the short- and long-term effects of enteral nutrition on postoperative PLC patients, and will discuss various aspects such as the protection of liver function, regulation of the immune system, short-term recovery, and long-term prognosis.

Early enteral nutrition may be used in the short-term rehabilitation process to hasten the recovery of gastrointestinal function, reduce the length of hospitalization, and minimize the incidence of postoperative infections and peritoneal effusion. The current evidence suggests that the mechanism of early enteral nutrition has developed over time as a standalone nutritional support strategy to become a major treatment option with both hepatoprotective and immunomodulatory effects. Concerning the protection of liver function, early enteral nutrition can greatly decrease the level of postoperative ALT, AST, and total bilirubin and raise the level of albumin and prealbumin, indicating specific benefits in stimulating the synthesis of hepatic proteins and repair of hepatocytes. In reference to the modulation of immune system function, enteral nutrition has been shown to increase the number of CD3⁺ and CD4⁺ T-cells and the CD4⁺/CD8⁺ ratio, and decrease the levels of inflammatory cytokines like TNF- α and IL-6; these effects are highly related to the preservation of the mucosal barrier integrity of the intestine and the alleviation of endotoxin translocation. Long-term prognosis is also associated with the state of malnutrition in PLC patients, and initial findings indicate that enteral nutrition could enhance the quality of life after surgery and long-term survival.

Nevertheless, there are also drawbacks to available studies. Initially, the absence of standardized guidelines on the types of enteral nutrition formulations, the timing of its initiation, and administration pathways used in various studies leads to significant heterogeneity in the results. Secondly, most studies have small sample sizes and short follow-up periods, and they do not contain adequate long-term information on survival and quality of life. Thirdly, the available enteral nutrition regimens are generally based on the general population of patients and thus cannot be tailored to meet the specific nutritional requirements of individual patients. Fourthly, there is a possibility of bias in a number of studies, where there is not sufficient

strong evidence yet to persuade clinicians that nutritional support has a definite long-term benefit among patients with liver disease.

Future studies must be aimed at performing high-quality randomized controlled trials with large sample sizes and long-term follow-up, development of standardized enteral nutrition intervention guidelines, and investigation of individualized nutritional approaches depending on gut microbiota modulation, with the definition of the ideal target population of various formulation types. Moreover, multi-omics technology needs to be used to clarify the underlying molecular pathophysiology of how enteral nutrition can enhance the prognosis of PLC surgery, and comparative studies comparing enteral nutrition and parenteral nutrition, and among different types of enteral nutrition formulations, need to be done to offer direct evidence to be used in making clinical decisions, thus providing more precise and clinically useful nutritional support regimens to postoperative PLC patients.

Disclosure statement

The author declares no conflict of interest.

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