

## Advancements in nutritional diagnosis and support strategies during the perioperative period for patients with liver cancer

Xiao-Qin Li, Yun Liang, Chen-Feng Huang, Sui-Ning Li, Lei Cheng, Chuan You, Yao-Xia Liu, Tao Wang

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade A, Grade B, Grade C, Grade C, Grade C

**Novelty:** Grade A, Grade B, Grade B, Grade B, Grade C

**Creativity or Innovation:** Grade A, Grade B, Grade B, Grade C, Grade C

**Scientific Significance:** Grade A, Grade B, Grade B, Grade B, Grade C

**P-Reviewer:** Adhoute X; Azer S; Rizzo A; Triantafillidis J

**Received:** March 8, 2024

**Revised:** May 27, 2024

**Accepted:** June 24, 2024

**Published online:** August 27, 2024

**Processing time:** 161 Days and 4.7 Hours



**Xiao-Qin Li, Lei Cheng, Chuan You,** Department of Hepatobiliary Surgery, The Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, Sichuan Province, China

**Yun Liang,** Department of Paediatric Surgery, The Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, Sichuan Province, China

**Chen-Feng Huang, Sui-Ning Li,** Department of Cardiovascular Surgery, The First Affiliated Hospital, Jinan University, Guangzhou 510632, Guangdong Province, China

**Yao-Xia Liu,** Department of Geriatric Endocrinology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu 610072, Sichuan Province, China

**Tao Wang,** Department of Pediatric Cardiology, West China Second University Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

**Tao Wang,** Department of Pediatrics, Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu 610041, Sichuan Province, China

**Co-corresponding authors:** Yao-Xia Liu and Tao Wang.

**Corresponding author:** Tao Wang, MD, Chief Physician, Department of Pediatric Cardiology, West China Second University Hospital, Sichuan University, No. 20 The 3<sup>rd</sup> Section, South Renmin Road, Chengdu 610041, Sichuan Province, China. [44871875@qq.com](mailto:44871875@qq.com)

### Abstract

Liver cancer represents a grave hepatic condition and constitutes a significant global health concern. Surgical resection remains the principal therapeutic modality for liver cancer. Nevertheless, perioperative malnutrition exerts a notable impact on patients with liver cancer, emerging as an independent risk factor for disease mortality and adverse outcomes. Hence, precise nutritional diagnosis and timely nutritional support hold the potential to enhance therapeutic efficacy and quality of life for liver cancer patients. This study represents a meticulous foray into the literature, extracting data from PubMed, Web of Science, and EMBASE databases, with a focus on the past 5 years. It scrutinizes the impact of malnutrition on patients undergoing liver cancer surgery, the etiological underpinnings of malnutrition within this patient cohort, the critical assessment of perioperative nutritional status, and the strategic approaches to nutritional

support. Utilizing rigorous inclusion and exclusion criteria, the amassed scholarly works are meticulously synthesized, methodically organized, and categorically elaborated upon. Ultimately, the authors propose the incorporation of a multidisciplinary nutrition management team during the perioperative period, comprising nutritionists, pharmacists, physicians, nurses, psychologists, and rehabilitation therapists, among other specialized professionals. Together, they collaborate to devise and implement personalized nutritional support plans, monitor patients' nutritional status, and make necessary adjustments as required. Through comprehensive management and intervention, improvements in the nutritional status of liver cancer patients can be achieved, thereby enhancing surgical success rates and facilitating postoperative recovery. It is believed that this manuscript will offer valuable insights to advance the nutritional management during the perioperative phase of liver cancer, aiding in ameliorating patients' nutritional status and treatment outcomes.

**Key Words:** Liver cancer; Nutritional diagnosis; Nutritional support; Perioperative period; Genetic testing; Immunonutrition; Probiotics and gut microbiota

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**Core Tip:** Liver cancer is a severe hepatic ailment, constituting a paramount global health concern. Nonetheless, the impact of perioperative malnutrition on patients with liver cancer is notably profound, emerging as an independent risk factor for disease mortality and adverse outcomes. This manuscript provides a comprehensive review focusing on the influence of malnutrition on liver cancer surgical patients, the etiology of malnutrition in liver cancer patients, perioperative nutritional status assessment, and nutritional support strategies. It is believed that this paper will offer reference opinions and theoretical groundwork to aid in the formulation of standardized perioperative nutritional support protocols.

**Citation:** Li XQ, Liang Y, Huang CF, Li SN, Cheng L, You C, Liu YX, Wang T. Advancements in nutritional diagnosis and support strategies during the perioperative period for patients with liver cancer. *World J Gastrointest Surg* 2024; 16(8): 2409-2425

**URL:** <https://www.wjgnet.com/1948-9366/full/v16/i8/2409.htm>

**DOI:** <https://dx.doi.org/10.4240/wjgs.v16.i8.2409>

## INTRODUCTION

Liver cancer is a major global health concern due to its high prevalence in many countries[1]. Primary liver cancer is the sixth most commonly diagnosed cancer and third leading cause of cancer-related deaths worldwide in 2020, with approximately 906000 new cases and 830000 deaths[2]. Liver cancer, a severe liver disease, entails the destruction of hepatic cells, resulting in abnormal liver function and metabolic disturbances. This leads to malnutrition symptoms such as hypoglycemia, hypoalbuminemia, and electrolyte imbalances. The heightened metabolic demands and compromised liver function in liver cancer patients contribute to their susceptibility to malnutrition, which subsequently weakens their immune function. Liver cancer treatment options are diverse and include surgical resection, liver transplantation, transarterial chemoembolization, ablation, neoadjuvant therapy[3-6]. However, surgical resection remains the primary treatment modality for liver cancer. Additionally, liver resection surgery, as a complex procedure, necessitates elevated nutritional requirements. Preexisting malnutrition impairs postoperative wound healing and increases the risk of infection[7]. Insufficient postoperative nutritional support further augments the likelihood of complications, prolongs patient recovery time, and exacerbates the financial burden. Malnutrition exerts a significant impact on liver cancer patients, emerging as an independent risk factor for disease mortality and adverse outcomes[8]. Accurate nutritional diagnosis and timely nutritional support can improve treatment efficacy and quality of life for liver cancer patients. This text aims to comprehensively explore the impact of malnutrition on patients undergoing liver cancer surgery, the causes of malnutrition in liver cancer patients, perioperative nutritional status assessment, and nutritional support strategies, providing reference opinions and theoretical basis for establishing standardized perioperative nutritional support protocols.

Firstly, a search strategy was employed: TS = ("liver cancer" OR "hepatic carcinoma" OR "hepatocellular carcinoma" OR "hepatoma" OR "liver neoplasm" OR "hepatic neoplasm" OR "hepatocellular cancer" OR "hepatic cancer") AND TS = (nutrition OR nutritional). The search was conducted in the electronic databases PubMed (<https://pubmed.ncbi.nlm.nih.gov>), Web of Science (WoS, <https://www.webofscience.com/wos>), and EMBASE (<https://www.embase.com>), with a publication year limit of the past 5 years. The search strategy aimed to include as many published articles as possible.

Selection was carried out by screening the titles and abstracts of all publications. The retrieved articles were manually categorized into four aspects: "impact", "causes", "assessment", and "treatment". They were then arranged in descending order based on their publication dates. If an article covered multiple aspects mentioned above, it was included multiple times.

The articles were independently reviewed by two authors who checked the inclusion and exclusion criteria. The inclusion criteria were as follows: (1) Articles with open access to abstracts and full texts; and (2) Articles written in English. The exclusion criteria were as follows: (1) Protocols and articles unrelated to the topic; (2) Conference pro-

ceedings; or (3) Animal experiments.

The factors contributing to early-stage malnutrition in liver cancer patients primarily depend on the extent of liver dysfunction, while late-stage malnutrition factors need to be considered in conjunction with tumor-related factors[9-13]. The main type of malnutrition observed in liver cancer patients is energy-protein deficiency. The primary reasons for this are as follows: (1) Reduced food intake: Symptoms such as early satiety, taste disturbances, abdominal distension, and diarrhea can significantly decrease the normal food intake; (2) Decreased nutrient absorption: Portal hypertension leads to congestion and edema of the gastric and intestinal mucosa, resulting in decreased autonomous neural regulation and weakened peristalsis, leading to reduced absorption capacity; (3) Excessive loss of nutrients: Ascites, gastrointestinal bleeding, infections, and other factors can cause significant protein loss; (4) Impaired liver function leading to decreased protein synthesis capacity: Increased utilization of branched-chain amino acids (BCAAs) by the body results in decreased uric acid production, increased fatty acid oxidation and ketone body production. Alterations in the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis: During the progression of liver cancer and cirrhosis, blood levels of GH increase, IGF-1 decreases, and the response of IGF-1 to GH declines, affecting nutritional metabolism[14]; (5) Abnormalities in nutrient metabolism: Liver dysfunction can lead to insulin resistance and glucose intolerance, reducing glycogen storage and oxidation. Impaired production and utilization of fatty acids and ketone bodies occur, along with increased protein breakdown and significant nitrogen consumption in the body[15]; and (6) Metabolic disorders of vitamins and trace elements: Inadequate intake and reduced absorption can result in deficiencies of zinc, selenium, and vitamins. The deficiency of various vitamins and trace elements can further exacerbate liver damage.

Impact of malnutrition on patients undergoing surgery for liver cancer: (1) Decreased immune function: malnutrition will lead to decreased function of the immune system, making patients more prone to infections and other complications. The body needs sufficient nutrition to support the recovery of immune function and wound healing after liver cancer surgery[16,17]; (2) Nutritional metabolic disorders: liver cancer patients are often accompanied by metabolic disorders, including protein metabolism disorders, energy metabolism disorders and microelement metabolism disorders. Malnutrition may aggravate these metabolic disorders and further damage liver function[18,19]; (3) Muscle wasting and weight loss: malnutrition can lead to muscle wasting and weight loss, which can impact patients' surgical tolerance and recovery capacity. After liver cancer surgery, the recovery period is crucial for patients, and maintaining a good nutritional status contributes to improving the speed and quality of postoperative rehabilitation[20,21]; and (4) Hence, maintaining a favorable nutritional status is of paramount importance for liver cancer surgical patients. During the perioperative period, nutritional support should be an integral component of comprehensive treatment.

## NUTRITIONAL DIAGNOSIS

Accurate nutritional diagnosis is a prerequisite for rational nutritional therapy. The conventional process of nutritional diagnosis, known as the two-tier nutritional diagnosis, comprises nutritional screening and nutritional assessment. In 2015, the Committee of Tumor Nutrition and Supportive Therapy of the Chinese Anti-Cancer Association proposed the concept of a three-tier diagnosis for malnutrition, which was further refined in 2020[22,23]. They recognized that the traditional two-tier diagnosis fails to fully assess the psychological, physiological, neurological, and spiritual changes brought about by malnutrition in patients. Therefore, they recommend conducting a comprehensive evaluation, namely the third-tier nutritional diagnosis, following nutritional assessment. Similarly, ESPEN and ASPEN have also incorporated the additional step of "extended assessment" (ESPEN) or "diagnosis" (ASPEN) after nutritional screening and assessment.

### Nutritional screening first-tier diagnosis

The definition of nutritional screening is the use of simple methods to quickly identify patients in the healthy population who may have underlying diseases without exhibiting symptoms[24]. According to ESPEN, it is the process of rapidly identifying patients in need of nutritional support among all patients[25]. Nutritional screening can swiftly identify liver cancer patients in need of nutritional support. Common methods mainly include the scale method including nutritional risk screening 2002 (NRS 2002), malnutrition universal screening tool (MUST), mini nutritional assessment-short form (MNA-SF), and the Royal Free Hospital Nutritional Prioritizing (RFH-NPT), Liver Disease Undernutrition Screening Tool (LDUST)[26-29].

**NRS 2002:** NRS 2002 was initially proposed by Kondrup *et al*[30], was refined by ESPEN in 2002[31]. It encompasses four key dimensions: fluctuations in body weight (weight and weight change), dietary intake (nutritional intake), the impact of the disease on patients (diseases), and age (age). It yields a total score of 7, whereby a score of  $\geq 3$  signifies the presence of nutritional risk in the patients[32]. A substantial body of research substantiates the heightened sensitivity of NRS 2002 in nutritional screening for individuals with liver cancer. However, it is worth noting the apparent limitations of NRS 2002, specifically its inclusion of body mass index (BMI) calculation, which renders it unsuitable for liver cancer patients who are unable to assume a standing position or have concomitant hepatic encephalopathy or ascites[33].

**The MUST:** MUST is a nutritional assessment tool proposed by Elia[34] from the United Kingdom in 2003[34]. It includes BMI (body weight), unintentional weight loss in the past 3-6 mo (weight change), presence of acute illness, or inability to eat for more than 5 d (diseases and nutritional intake). The scores are categorized into low risk, medium risk, and high risk. Research by Stratton *et al*[35] has shown that MUST is more sensitive in predicting the mortality and hospitalization time of elderly patients. Raslan *et al*[36], in a comparative study with NRS 2002 on hospitalized patients, found that the correlation of MUST results with clinical outcomes is inferior to that of NRS 2002. Currently, the application of MUST in

nutritional screening for liver cancer is less common[37].

**The MNA-SF:** MNA-SF is a simplified version of the original Mini Nutritional Assessment developed by French nutritionist Guigoz *et al*[38] in 2005. It primarily evaluates weight changes, nutritional intake, the impact of diseases on patients, motility, and other factors such as appetite, psychological stress, mental state, and calf circumference (CC). Its purpose is to provide a rapid and effective method for assessing the nutritional status of elderly individuals. It has been widely used in clinical practice and research to help identify and intervene in the nutritional issues of elderly individuals, thus improving their nutritional and overall health status[28,39,40].

**The RFH-NPT:** The RFH-NPT is specifically developed for patients with chronic liver disease and is considered suitable for nutritional risk screening in patients with liver cirrhosis. The assessment includes weight changes, nutritional intake, considerations for fluid retention and so on. RFH-NPT is more sensitive than NRS 2002 in identifying liver disease patients at risk of malnutrition[41-43]. The 2019 ESPEN guidelines recommend RFH-NPT as the preferred nutritional screening tool for liver disease patients.

**The LDUST:** LDUST is a tool used to assess the presence of malnutrition in patients with liver disease. It includes aspects of weight change, nutritional intake, mobility, fluid retention, and muscle and fat status in patients with liver disease[44].

The LDUST is a quick, convenient, and easy-to-complete screening tool that is more effective in detecting malnutrition in cirrhotic patients than commonly used nutritional screening tools. The tool has been evaluated and validated by nutritionists. In addition, the study recommended that all hospitalized patients with cirrhosis should be evaluated by a dietitian due to the high prevalence of malnutrition in hospitalized patients with cirrhosis[45]. The American Society for Parenteral and Enteral Nutrition and the Academy of Nutrition and Dietetics have unanimously recognized the strong association between these factors and malnutrition in a consensus statement[46].

The aforementioned nutritional screening tools assess patients' weight changes and nutritional intake. NRS 2002, MNA-SF, and RFH-NPT evaluate the impact of disease on patients, while MNA-SF and LDUST assess patients' functional capacity. RFH-NPT and LDUST also consider the influence of fluid retention. Additionally, NRS 2002 includes age as a screening factor, MNA-SF includes appetite, psychological stress, mental state, and CC, and LDUST includes fats and muscle. RFH-NPT and LDUST are modified scales designed specifically for nutritional screening in patients with liver diseases, taking into account the characteristics of the disease and catering to specialized needs compared to other scales (Table 1).

Nutritional status is fundamental to a patient's overall well-being[47]. Liver cancer patients should undergo routine nutritional screening within 24 h of admission, performed by the nurse handling the admission procedures. For patients with negative nutritional screening results, screening should be repeated after one treatment course. For patients with positive nutritional screening results, nutritional assessment should be conducted, and a nutritional treatment plan or education should be developed. Currently, China has made positive nutritional screening a prerequisite for the use of enteral and parenteral nutrition preparations and medical insurance coverage[48].

However, nutritional screening has a higher false-negative rate in special patient populations such as cancer patients, critically ill patients, and elderly patients (age  $\geq 65$ )[23]. Regardless of the initial diagnostic result from nutritional screening, routine nutritional assessment should be conducted. Therefore, for patients with liver cancer, direct nutritional assessment is recommended to reduce the rate of underdiagnosed malnutrition in this population.

### **Nutritional assessment - secondary level diagnosis**

For patients who have tested positive on nutritional screening, a secondary level diagnosis, known as nutritional assessment, should be conducted. Special populations such as cancer patients, critically ill individuals, and the elderly ( $\geq 65$ -years-old) should undergo routine nutritional assessment, regardless of the results of the primary level diagnosis (nutritional screening), as nutritional screening tends to have a higher false-negative rate in these populations[49,50]. Nutritional assessment should be conducted by a qualified nutrition professional (such as a nutrition nurse, dietitian, or oncologists) within 48 h of the patient's admission[51]. Common methods used include nutritional assessment scales, dietary surveys, anthropometric measurements, and estimations of energy requirements.

**Nutritional assessment scales:** The commonly used nutritional assessment scales include subjective global assessment (SGA), patient-generated SGA (PG-SGA), Royal Free Hospital Global Assessment (RFH-GA) and the Global Leadership Initiative on Malnutrition (GLIM).

**SGA:** SGA was initially designed in 1984 to evaluate the nutritional status of patients receiving parenteral nutrition. The assessment includes weight changes, dietary changes, gastrointestinal symptoms, functional capacity, metabolic stress, physical examination findings such as triceps skinfold thickness (TSF) and ankle edema. It has been widely used in clinical practice and is a simple yet effective nutritional assessment tool applicable to outpatient and inpatient populations of different diseases and age groups[52].

SGA combines subjective feedback from patients and objective evaluations from healthcare professionals. Its reliability and validity have been extensively tested, making it the gold standard for nutritional assessment. SGA is suitable for various patient populations, including those with hepatic cirrhosis, liver cancer, liver transplantation, and long-term dialysis, as it is simple to administer, repeatable, applicable to a wide range of patients, easy to learn, and not influenced by sodium and water retention[53] (Table 2).

Regarding weight changes, if there has been a significant change over the past 6 mo or recent 2 wk, but no loss or gain in the past month, or if weight has stabilized after treatment in the past 2 wk, weight loss should not be considered.

**Table 1** Nutritional screening-first-tier diagnosis tools comparison

Feature	NRS 2002	MUST	MNA-SF	RFH-NPT	LDUST
Age	√				
Diseases	√	√		√	
Weight	√	√	√	√	
Weight change	√	√	√	√	√
Nutritional intake	√	√	√	√	√
Appetite			√		
Motility			√		√
Psychological stress			√		
Mental stat			√		
Fluid retention				√	√
Fats					√
Muscle					√
Calf circumference			√		

√ Indicates that the content is included in the assessment form. LDUST: Liver disease undernutrition screening tool; MNA-SF: Mini nutritional assessment-short form; MUST: Malnutrition universal screening tool; NRS 2002: Nutritional risk screening 2002; RFH-NPT: Royal Free Hospital nutritional prioritizing.

**Table 2** Subjective global assessment

Indicator	A	B	C
	Optimal nutritional status	Mild to moderate malnutrition	Severe malnutrition
Recent weight change	None/increase	Decrease of less than 5%	Decrease of more than 5%
Modification in dietary habits	None	Reduction	Abstaining from food/low-calorie liquid diet
Gastrointestinal symptoms	None/decreased appetite	Mild nausea, vomiting	Severe nausea, vomiting
Change in mobility	None/decreased	Able to walk out of bed	Bedridden
Stress response	None/low degree	Moderate degree	High degree
Muscle depletion	None	Mild	Severe
Triceps skinfold thickness in mm	Normal	Slight decrease	Significant decrease
Ankle swelling	None	Mild	Severe

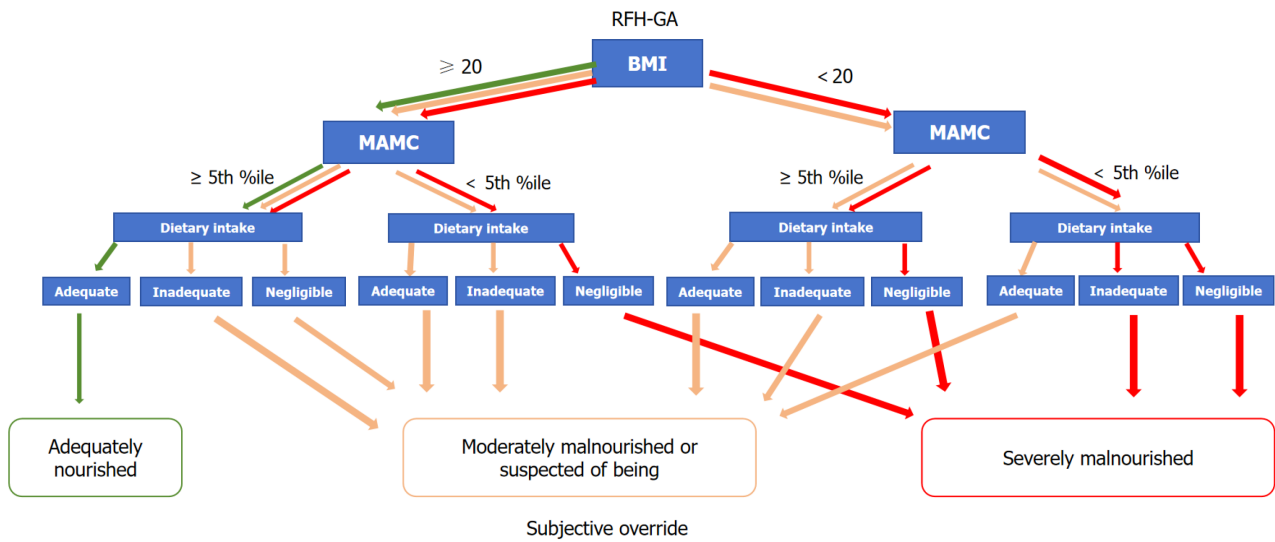
Gastrointestinal symptoms should persist for at least 2 wk; occasional occurrences once or twice should not be considered.

Stress reference: Extensive burns, high fever, or significant bleeding are considered high stress; prolonged fever or chronic diarrhea are considered moderate stress; long-term low-grade fever or malignant tumors are considered low stress.

If five or more items in the evaluation results are classified as grade C or grade B, it can be diagnosed as severe or moderate malnutrition.

RFH-GA: In 2006, the Royal Free Hospital in London expanded upon SGA by adding BMI, mid-arm muscle circumference (MAMC), and dietary components, creating the modified SGA (RFH-GA). This modified version is specifically used to assess the nutritional status of end-stage liver disease patients and has improved its accuracy to some extent[54] (Figure 1).

The RFH-GA incorporates both subjective and objective variables to assess nutrition, including BMI, MAMC and dietary intake. In the case of fluid retention, BMI needs to be corrected for the patient's dry weight, commonly estimated by the postparacentesis body weight or the weight recorded before fluid retention if available, or by subtracting a percentage of the weight based upon the severity of the ascites (mild 5%, moderate 10%, and severe 15%), with an additional 5% subtracted if bilateral pedal oedema is present, as described in several studies. Then the dry-weight BMI is calculated by dividing the patient's estimated dry weight (kg) by the square of the patient's height (m). The TSF (mm) and mid-arm circumference (MAC, cm) were measured using Holtain/Tanner-Whitehouse skinfold calipers. These two measurements are used to calculate the MAMC:  $MAMC (cm) = MAC (cm) - [3.14 \times TSF (cm)]$ . Measures of the MAMC



**Figure 1 Royal Free Hospital global assessment.** Adapted from Morgan *et al*[54] (Supplementary material). BMI: Body mass index; MAMC: Mid-arm muscle circumference.

below the 5<sup>th</sup> percentile are indicative of a risk of malnutrition.

**PG-SGA:** PG-SGA is an improved nutritional assessment method based on SGA, specifically designed for cancer patients[55]. It has received strong recommendations from organizations such as the American Dietetic Association[56]. PG-SGA includes assessments from both the patient and healthcare professionals, with a total of seven sections. The patient assessment consists of four parts: body weight, dietary intake, subjective symptoms, and activity and physical function. The healthcare professional assessment includes three parts: disease and nutritional requirements, metabolic needs, and physical examination. The assessment results of PG-SGA can be categorized into qualitative and quantitative evaluations, with the quantitative assessment being the major highlight of PG-SGA[57]. Studies conducted by Gabrielson *et al*[58] have shown that when PG-SGA was applied to cancer patients in outpatient settings, it achieved a sensitivity of 97.0% and specificity of 86.0%. When using PG-SGA for nutritional evaluation of liver cancer patients, it is recommended to provide training in order to identify patients' nutritional deficiencies at an earlier stage and ensure timely nutritional therapy[59] (Table 3).

**Nutritional grading recommendations:** the total score is used to determine specific nutritional interventions, including patient and family education, symptomatic treatment including medication interventions, and appropriate nutritional interventions (dietary modifications, nutritional supplements, enteral nutrition, parenteral nutrition). First-line nutritional intervention involves optimal symptom management.

0-1: No intervention required at present, reassessment and standard treatment.

2-3: Nutritional analysis by a dietitian, nurse, or other healthcare professional, followed by appropriate education for the patient and their family.

4-8: Requires intervention by a dietitian, with assistance from nurses and doctors.

≥ 9: Urgent need for symptom management and/or nutritional intervention.

**GLIM:** The GLIM is a multidisciplinary working group composed of experts from the international nutrition community. It was established in 2016 with the aim of improving global understanding and management of malnutrition. GLIM focuses on developing a consensus approach to the identification, assessment, and management of malnutrition [60].

By bringing together experts from different disciplines and leveraging their collective knowledge and expertise, GLIM aims to advance the field of malnutrition management and contribute to improved outcomes for individuals affected by malnutrition[61].

GLIM is a relatively concise set of assessment criteria, making it more convenient to use compared to other assessment tools[62]. However, there is currently no unified standard for assessing muscle mass, and the reliability and validity of GLIM are being extensively validated from various perspectives. The reliability and validity of GLIM are currently undergoing extensive validation from various perspectives. The goal is to ensure that GLIM provides accurate and reliable assessments of malnutrition[63-65] (Table 4).

The aforementioned nutritional assessment tools are commonly employed in practical applications. However, it is important to note that the GLIM, despite its recent introduction, still requires extensive validation from multiple sources. The SGA is applicable for nutritional assessment in almost all hospitalized patients. Nonetheless, due to its limited consideration for specific diseases and circumstances, derived tools such as the PG-SGA and RFH-GA have been developed based on the SGA. The PG-SGA is better suited for assessing patients with tumors, while the RFH-GA primarily focuses on liver disease patients.

**Dietary assessment:** Dietary assessment is commonly conducted using dietary assessment software and the 24-h dietary recall method. Through dietary assessment, healthcare professionals can gain insights into a patient's nutrient intake and calculate their daily energy intake. This information can help determine the type of malnutrition a patient may be experi-

**Table 3 Patient-generated subjective global assessment**

Feature	Patient self-assessment				Medical staff assessment			
	Weight change	Food intake	Gastrointestinal symptoms	Activities and functions	Diseases and Age	Metabolic emergency	Physical fitness (muscle, fat, body fluids)	
Score	0-5	0-5	0-23	0-3	0-6	0-9	0-3	

**Table 4 Global leadership initiative on malnutrition**

Phenotypic indicators		Etiological indicators		
Involuntary decline in body mass	Reduction in BMI	Decrease in muscle mass	Decreased food intake or impaired digestion and absorption	Inflammation or disease burden
Body mass reduction exceeding 5% within a span of 6 mo	Below 20 kg/m <sup>2</sup> for individuals under 70 yr of age; below 22 kg/m <sup>2</sup> for individuals aged 70 and above (according to European and American standards)	None	Food intake below 50% of energy requirements for more than 1 wk	Acute illness or injury
Body mass reduction exceeding 10% over a period of more than 6 mo	Below 18.5 kg/m <sup>2</sup> for individuals under 70 yr of age; below 20 kg/m <sup>2</sup> for individuals aged 70 and above (according to Asian standards)		Food intake reduction for more than 2 wk	Chronic disease
–	–		Any gastrointestinal symptoms that affect digestion and absorption	

–: Intentionally blank, no information. BMI: Body mass index.

encing, such as energy deficiency, protein deficiency, or a mixed type[66].

Dietary assessment software provides a systematic approach to collecting and analyzing dietary data, allowing for a comprehensive evaluation of nutrient intake[67-69]. The software often includes a food database that contains nutritional information for various foods and allows for the calculation of nutrient intake based on the reported food consumption.

The 24-h dietary recall method involves asking the patient to recall all the foods and beverages consumed in the past 24 h[70,71]. This method provides a snapshot of the patient's recent dietary habits and allows for a detailed assessment of nutrient intake.

By conducting dietary assessments, healthcare professionals can identify deficiencies or excesses in specific nutrients and develop tailored nutritional interventions to address the patient's specific needs. Additionally, dietary assessments can monitor changes in dietary patterns over time, evaluate the effectiveness of dietary interventions, and guide nutritional counseling and education.

**Anthropometric measurements:** In addition to height, weight, and BMI, there are several other anthropometric measurements that can be used to assess body composition and muscle mass. These measurements include non-dominant MAC, MAMC, TSF thickness, hand grip strength (HGS), and bilateral CC.

TSF, MAC, and MAMC are anthropometric measurements used to assess muscle and fat mass in the human body. These measurements are less susceptible to the influence of sodium and fluid retention and are positively correlated with the severity of liver cirrhosis and liver cancer. Therefore, they have become relatively accurate indicators for evaluating malnutrition in end-stage liver disease patients[72]. HGS is a simple and sensitive method for evaluating muscle function. It is not influenced by sodium and fluid retention, and the test results are reliable. Handgrip strength is well-correlated with upper arm circumference in assessing muscle reserve, making it an effective method for independently predicting malnutrition in end-stage liver disease patients. It is also a good indicator for predicting complications in liver cirrhosis and liver cancer[73]. Some researchers suggest performing dynamic handgrip strength tests using the non-dominant hand, as this method is more reliable in clinical practice[59]. However, this testing method is not suitable for patients with impaired consciousness or hepatic encephalopathy. Recent studies have shown that handgrip strength testing is more sensitive than upper arm circumference and TSF in detecting malnutrition in liver disease patients[74].

Anthropometric measurements provide valuable information about body composition and muscle function, allowing healthcare professionals to assess nutritional status and monitor changes over time. These measurements, along with other assessment tools, contribute to a comprehensive evaluation of a patient's nutritional health.

**Energy requirements:** The energy requirements of patients encompass resting energy expenditure (REE), basal energy expenditure, and total energy expenditure. There are various methods for measuring energy requirements, including direct calorimetry, indirect calorimetry (IC), and estimation equations. Direct calorimetry is primarily used in laboratory settings, while IC and energy estimation equations are commonly employed in clinical practice[75,76].

IC is a method used to measure the energy expenditure in the human body. It estimates the metabolic rate by measuring the oxygen consumption and carbon dioxide production in exhaled gases. IC is considered the gold standard

for accurately assessing the REE of each patient. Ideally, any patient with uncertain energy requirements should undergo this measurement. By doing so, it can prevent underfeeding, overfeeding, and their associated complications[77].

Estimation equations, such as the thumb rule or formula methods, are commonly used to estimate energy requirements. The Harris-Benedict equation is a classic example, although the Mifflin-St Jeor equation is currently recommended. Estimation equations are simple, convenient, and easy to use. However, it is important to note their limitations, as they are less accurate than IC and may not be suitable for patients requiring precise measurement of energy expenditure[78,79].

Using nutritional assessment, patients can be classified into two categories: those with and without malnutrition. Patients without malnutrition do not require nutritional intervention. However, for patients with malnutrition, it is important to assess the severity and implement further comprehensive evaluations or initiate nutritional therapy accordingly. Regardless of the presence of malnutrition, a follow-up nutritional assessment should be conducted after completing one course of treatment for the underlying condition.

### **Comprehensive evaluation - third level diagnosis**

During this stage, the underlying causes of malnutrition in liver cancer patients can be identified through the analysis of patient medical history, physical examination, laboratory tests, and instrumental examinations. Factors such as reduced intake, absorption disorders, increased demand, and enhanced energy expenditure can be identified. Based on the energy expenditure level, stress, inflammatory response, and metabolic status, appropriate nutritional support strategies can be formulated.

**Medical history inquiry:** Emphasis should be placed on the nutrition-related medical history of liver cancer patients such as changes in food intake, gastrointestinal symptoms, and weight fluctuations. The Karnofsky Performance Status score is commonly used to assess the physical activity capacity of liver cancer patients[80]. Quality of life surveys can be conducted using tools like the European Quality of Life-5 Dimensions[81] scale and the Quality of Life Core Questionnaire. Liver cancer patients with severe malnutrition often experience mental and psychological effects, with depression being particularly common, and older individuals may also exhibit cognitive impairments. Psychological assessment tools such as the Hospital Anxiety and Depression Scale[82] and the Patient Health Questionnaire can be utilized.

**Physical examination and fitness assessment:** During nutritional physical examination of liver cancer patients, special attention should be given to assessing muscle mass, fat deposition, edema, and ascites. Physical performance measurements may include the 6-min walk test (cardiorespiratory endurance)[83], 30-s chair stand test (muscular endurance), isometric knee extension (lower limb strength)[84], single-leg standing time (static balance), and maximum stride length (dynamic balance/coordination)[85], among others.

**Laboratory indicators:** (1) Blood glucose: elevated blood glucose levels in liver cancer patients (excluding those with diabetes) often indicate a stress response; (2) Lymphocyte count: it can indirectly reflect the nutritional and immune status of liver cancer patients. However, it is influenced by factors such as infection, sodium and fluid retention, tumor cell growth, splenic hyperfunction and liver cirrhosis, which limits its evaluation value; (3) Inflammation levels: elevated levels of tumor necrosis factor alpha, interleukin 1, interleukin 6, C-reactive protein (CRP), thiobarbituric acid reactive substances, and superoxide dismutase indicate the presence of an inflammatory response, which can contribute to the complexity of malnutrition in liver cancer patients. Studies have found that an increase in CRP levels has a greater predictive value for the prognosis of cancer patients compared to decreased albumin levels[86]. The relationship between Glasgow Prognostic Score (GPS) results and the survival of hepatocellular carcinoma patients is closely linked[87]. Elevated GPS (1-2) serves as an independent prognostic indicator for overall survival in liver cancer patients after surgical resection. Patients with higher GPS experience poorer overall survival[88]; (4) Albumin: Albumin serves as a commonly employed nutritional indicator; however, its evaluation in liver cancer patients is impeded by the prevalent occurrence of hypoalbuminemia and ascites, which compromise the accuracy of measurements. Furthermore, exogenous blood products can also impact albumin levels. Consequently, the utility of albumin in assessing the nutritional status of liver cancer patients is relatively diminished. A study conducted by Ferreira *et al*[89] encompassed statistical analyses of patients with liver cirrhosis and liver cancer awaiting liver transplantation, affirming the limited correlation between albumin levels and nutritional status. This observation underscores the inadequacy of relying solely on albumin levels to evaluate the nutritional status of liver cancer patients. Hence, a comprehensive assessment incorporating other clinical and laboratory indicators is imperative to obtain a more comprehensive and precise evaluation[89]; (5) Prealbumin: It represents the precursor form of albumin, with a half-life of 1.9 d. In comparison to albumin, prealbumin exhibits heightened sensitivity to changes and remains unaffected by exogenous blood products. Consequently, it can serve as an evaluative marker for malnutrition in liver cancer patients. However, the levels of prealbumin can be influenced by hepatic reserve function, feeding status, and sodium and water retention, thereby diminishing its value in nutritional assessment[90]; (6) Creatinine height index: It is the ratio of 24-h urinary creatinine to height and accurately reflects the state of protein synthesis and breakdown in the body. A value of 60%-80% or less than 60% can be used as an evaluation criterion for moderate and severe protein deficiency. It is not affected by sodium and water retention and serves as a sensitive indicator for nutritional evaluation in liver cancer patients with normal renal function and no infection[91]; (7) Prognostic nutritional index (PNI): It is calculated based on the levels of albumin and total lymphocyte count. It is categorized into low, moderate, and severe risk groups. Research has shown that PNI is significantly correlated with overall survival and recurrence-free survival in liver cancer resection patients. A low PNI can serve as an effective marker for predicting the prognosis of such patients[92]; and (8) Monitoring of liver and kidney function in liver cancer patients, as well as the assessment of intestinal barrier function (diamine oxidase, D-lactate, and bacterial endotoxins), helps understand the metabolism of factors and their products (protein catabolism inducers, fat mobilization factors, free fatty



acids, glucose, and lactate), which aids in determining the absorption of nutrients and guides the development of appropriate nutritional plans for patients.

**Instrument inspection:** Dual-energy X-ray, magnetic resonance imaging, computed tomography, and B-mode ultrasound examinations can offer insights into the composition of lean body tissue and adipose tissue in patients. However, these diagnostic methods are constrained in their broader application to liver cancer patients due to their elevated cost and the expertise required for their administration and interpretation.

**Bioelectrical impedance analysis:** On the other hand, is a widely used, simple, non-invasive, and convenient method in clinical practice[93]. Bioelectrical impedance analysis (BIA) is a technique that measures body composition by utilizing the electrical properties and variations of biological tissues and organs. It can provide information about fat mass, body fat percentage, non-fat mass, skeletal muscle mass, estimated bone mass, protein mass, water content, water percentage, extracellular fluid volume, intracellular fluid volume, basal metabolic rate, phase angle, visceral fat level, body shape, and more. Phase angle, in particular, has been identified as an important predictive factor for nutritional status. Since the phase angle of the trunk tends to be larger, it is recommended to measure the phase angle of the arms and thighs[94].

Research by Cotogni *et al*[95] has shown that BIA is a useful tool for analyzing the nutritional status and survival rate of cancer patients. Both are related to changes in cell membrane integrity and fluid balance, and the phase angle reflects changes in soft tissue quality and quantity (*i.e.* cell membrane permeability and soft tissue hydration). The phase angle can also be used for preoperative volume assessment to reduce blood loss during liver resection. Dzierżek *et al*[96] have also demonstrated that in advanced pancreatic cancer patients, the phase angle is a more effective survival indicator compared to traditional nutritional assessment markers such as albumin, prealbumin, and transferrin. Patients with low preoperative phase angles had significantly higher rates of severe postoperative infections and mortality compared to those with normal or high phase angles[97].

**Genetic testing:** In recent years, genetic testing has been widely used in clinical medicine. With the continuous development of genetics and genomics research, genetic testing is guiding the progress of predictive medicine and being applied in various aspects such as disease prevention, genetic diagnosis, and personalized medicine.

Through genetic metabolic capacity testing, it is possible to discover an individual's ability to absorb, metabolize, and store nutrients in the body. This information can guide the selection of nutritional support substances, quantities, and routes. By analyzing specific genes related to nutrient metabolism, such as those involved in the metabolism of vitamins, minerals, carbohydrates, fats, and proteins, genetic testing can provide insights into an individual's unique nutritional requirements and responses[98-101].

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## NUTRITIONAL SUPPORT STRATEGIES

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The perioperative nutritional support for malnourished patients with liver cancer encompasses both preoperative and postoperative phases. Precise and well-designed nutritional support plays a crucial role in promoting patient recovery and improving clinical outcomes.

### **Preoperative nutritional support strategies for liver cancer patients**

In 2017, the European Society for Clinical Nutrition and Metabolism published guidelines that emphasized the importance of preoperative nutritional support for patients with severe malnutrition or significant nutritional risk, even if it necessitates delaying the surgery[102]. Administering preoperative nutritional support to liver cancer patients at risk of malnutrition has shown various benefits, including improved nutritional status, enhanced liver function, faster gastrointestinal recovery, and reduced complications.

**Nutritional support time:** The duration of preoperative nutritional support for liver cancer patients should be determined based on their nutritional status and the timing of the surgery. Short durations may not effectively achieve the desired nutritional support. Current guidelines recommend short-term nutritional support of 7-10 d for patients with mild malnutrition, while patients with moderate to severe malnutrition may require longer support of 10-14 d, combined with resistance exercise. Studies have shown that providing preoperative nutritional support for liver cancer patients at nutritional risk for 7-10 d improves their nutritional status and reduces the incidence of postoperative intra-abdominal fluid accumulation[103,104]. In a study by Fukuda *et al*[105], preoperative nutritional support for malnourished cancer patients for more than 10 d resulted in a significantly lower occurrence of postoperative infections compared to support durations less than 10 d or no nutritional support at all.

**Modes of nutritional support:** The preoperative nutritional support for liver cancer patients should be tailored to their specific conditions, such as disease status, appetite, nutritional status, and gastrointestinal tolerance. The preferred approach is nutritional health education, which is conducted by specialized nurses or dietitians and is integrated throughout the various stages of nutritional support[106]. When nutritional health education is insufficient to meet the patient's nutritional needs or in cases of moderate malnutrition, oral nutritional supplementation (ONS) can be considered[107]. Compared to enteral and parenteral nutrition, oral supplementation has higher compliance[108]. It is recommended to use high-protein oral nutritional supplements or immune nutrition, with a suggestion to ensure three oral supplementations per day, providing a minimum of 400-600 kcal of energy[109]. When patients are unable to meet their nutritional needs through ONS, enteral nutrition should be administered *via* a feeding tube for a minimum of 7 d. If

intolerance symptoms occur during the nutritional support process (such as abdominal distension, abdominal pain, significant reduction in anal gas and bowel movements, gastric residual volume > 500 mL, abnormal abdominal imaging, *etc*), reducing or temporarily suspending oral nutrition and diet should be considered[110]. If ONS and enteral nutrition fail to meet protein and/or calorie requirements (less than 50% of recommended intake), preoperative parenteral nutrition support is advised to improve nutritional status. Enteral nutrition supplementation provides anti-inflammatory stimulation to the intestinal mucosa-associated lymphoid tissue, promotes the secretion of immunoglobulin A, helps maintain the mucosal barrier, and prevents the movement of bacterial microorganisms into the portal venous system, thus reducing the risk of infection and complications[111]. Total parenteral nutrition is suitable for patients with severe malnutrition and gastrointestinal dysfunction[112]. The choice of preoperative nutritional support mode should adhere to the five-step principle of nutritional support, tailored to the patient's specific needs[106]. However, in clinical practice, due to the invasive nature of enteral nutrition through tube feeding, it may cause patient discomfort and alter their perception of well-being. Patients and their families may have low acceptance of preoperative invasive nutrition support. Therefore, in practical terms, preoperative nutritional support for patients with moderate to severe malnutrition often involves a combination of partial enteral and partial parenteral nutrition support.

**Selection of nutritional support substances and quantities:** (1) Energy: The daily energy intake for liver cancer patients should aim to alleviate catabolic metabolism and endogenous protein hydrolysis. During the stable phase, the recommended energy intake for non-obese liver cancer patients (BMI < 18.5 kg/m<sup>2</sup>) can be based on the guidelines provided by the European Association for the Study of the Liver, suggesting an energy intake of ≥ 35 kcal/kg/d (based on corrected actual body weight after fluid retention) or 1.3 times the REE. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends 30-35 kcal/kg/d[113], while the Chinese Medical Association suggests an intake of 30-35 kcal/kg/d or 1.3-1.4 times the REE for patients with liver cirrhosis in China[114]. To prevent refeeding syndrome, initial energy intake should be reduced for liver cancer patients with moderate to severe malnutrition, generally following a standard of 20-25 kcal/kg/d[115]. If the patient's malnutrition is severe and of long duration, the initial energy intake should be further reduced to 10-15 kcal/kg/d[116]; (2) Protein: Excessive protein consumption is one of the characteristics of liver cancer patients. The daily protein requirement depends on the metabolic capacity and protein consumption levels in the patient's body. Liver damage leads to increased aromatic amino acids (AAAs) and decreased BCAAs, which may cause hepatic encephalopathy or other neurological complications[107]. Therefore, guidelines recommend a protein intake of 1.2-1.5 g/kg/d for liver cancer patients, along with an increased intake of BCAA to adjust the BCAA to AAA ratio. Studies have found that increasing dietary BCAA intake can improve liver function reserve and albumin levels in patients[117]; (3) Lipids: Lipids are an important source of calories for malnourished patients, accounting for 40%-50% of the total energy intake[118]. Due to impaired lipid metabolism in liver cancer patients, incomplete metabolism of long-chain triglycerides often occurs. It is recommended to use medium-chain triglycerides as an alternative form of lipid, which does not require bile salt absorption and can provide calories for patients with poor lipid absorption[53]; (4) Carbohydrates: Carbohydrates should account for 50%-60% of the total energy intake[103]. Liver cancer patients have a reduced glycogen storage and impaired gluconeogenesis, increasing the risk of hypoglycemia. A 12-h fasting period for these patients is equivalent to 2-3 d of fasting for healthy individuals[119]. Liver cancer patients can follow the principle of "small and frequent meals" and have a supplementary meal before bedtime to alleviate impaired glucose metabolism[120]; and (5) Vitamins: Due to reduced oral intake and impaired liver function, vitamin deficiencies are common in these patients. For example, patients with bleeding tendencies should be supplemented not only with water-soluble and fat-soluble vitamins but also with vitamin K. Patients with liver cirrhosis who use diuretics experience increased loss of water-soluble vitamins with increased urine output, necessitating enhanced supplementation[121].

**Immunonutrition:** Immunonutrition primarily involves the supplementation of substances that contribute to immune function, such as arginine, glutamine, omega-3 fatty acids, and nucleotides. Arginine is considered an enhancer of T lymphocytes, while glutamine provides oxidative fuel for lymphocytes and macrophages. Nucleotides enhance the host cell's defense capability[122]. These substances help control inflammation and reduce the risk of systemic inflammatory response syndrome during the treatment of malignant tumors. Studies have shown that postoperative inflammation, immune suppression, and liver dysfunction can be improved through preoperative immunonutrition[123]. However, the immunonutrition group and enteral nutrition group showed no statistically significant differences in postoperative complications and length of hospital stay. Russell *et al*[124] found no advantage in providing 5 d of immunonutritional support compared to the enteral nutrition group in patients undergoing liver resection with relatively good nutritional status. On the other hand, a meta-analysis indicated that immunonutrition is more suitable for malnourished patients, as malnutrition and immune suppression increase the risk of infection and death. Immunonutritional support can minimize early postoperative inflammatory response[122]. Since the immunonutrients take around 5 d to exert their effects on modulating immune and inflammatory responses in the body, it is recommended to use immunonutritional substances preoperatively.

**Probiotics and gut microbiota:** The gut microbiota is a vast and complex ecosystem consisting of approximately 10<sup>13</sup> to 10<sup>14</sup> microorganisms, with over 1000 different species, accounting for about 80% of the total microbial population in the body. It plays a significant role in the metabolism and absorption of nutrients such as carbohydrates, lipids, proteins, dietary fibers, and trace elements. The portal vein system, which receives venous blood from the intestines, is closely connected to the liver, forming the "gut-liver axis." When bacterial translocation occurs, the increased levels of endotoxins in the portal vein directly affect liver parenchymal cells, Kupffer cells, and immune cells, leading to the release of a series of inflammatory and cytokine factors by neutrophil aggregation, further aggravating liver damage. Numerous complica-

ations associated with gut dysbiosis, decreased colonization ability, bacterial translocation, such as gut-derived endotoxemia, spontaneous bacterial peritonitis, hepatic encephalopathy, are closely related and directly impact the patient's quality of life and prognosis[125,126].

The use of probiotics containing bifidobacteria, lactobacilli, butyric acid bacteria, lactulose, and other probiotic preparations can effectively promote the production of lactic acid in the intestine, inhibit the growth of pathogenic bacteria, maintain an anaerobic environment in the gut, reduce bacterial translocation and endotoxin production, decrease blood ammonia levels, improve liver function, and prognosis[127,128].

Fecal microbiota transplantation involves the transplantation of functional fecal microbiota derived from healthy individuals into the patient's intestinal tract, aiming to reconstruct a new gut microbiota and treat both intestinal and extraintestinal diseases. This revolutionary therapeutic approach has been proven highly effective in the treatment of refractory *Clostridium difficile* infection. Furthermore, it has demonstrated favorable therapeutic effects in various conditions, including enteritis, obesity, food allergies, multiple sclerosis, and Parkinson's disease[129,130].

### Postoperative nutritional strategies

It is recommended that liver cancer patients adopt the concept of enhanced recovery after surgery during the perioperative period[131]. Water intake should be restricted for 2 h before anesthesia, and fasting should be observed for 6 h before anesthesia to prevent patients from entering a catabolic state prematurely. Unless there are specific circumstances, patients undergoing liver resection can start drinking water on the day of surgery and progress to a clear liquid diet after 12 h postoperatively, gradually transitioning to a normal diet once anal gas passage and bowel sounds have resumed [132]. Randomized controlled trials have shown that ONS can improve the postoperative nutritional status of liver cancer patients, promote intestinal function recovery (indicated by the return of bowel sounds), shorten hospital stay, and accelerate postoperative recovery[133]. Adequate protein intake should be ensured in the early postoperative period, and it is recommended to increase protein intake through oral nutrition or meals on the day of surgery. Sufficient protein intake is more important than caloric intake in the early postoperative period. The selection of protein sources should be consistent with the preoperative period.

**Selection of nutrients:** Postoperative nutritional support aims to not only continue the preoperative nutritional support but also prevent the risk of malnutrition resulting from the surgical procedure itself. Randomized controlled clinical trials have found that the addition of total protein-medium chain triglycerides, an enteral nutrition suspension rich in protein and medium-chain triglycerides, can improve postoperative recovery in patients undergoing primary liver cancer resection[134]. It significantly reduces the time to first flatus and first bowel movement. Daily ONS with an energy supply of 400-600 kcal has been shown to significantly improve patient survival and liver function while reducing the incidence of postoperative complications[102]. Currently, postoperative nutrition support often advocates for low-calorie intake to avoid adverse effects caused by excessive caloric supply to the body[104].

**Methods of nutritional support:** Postoperative nutritional support follows the five-step ladder principle. If neither oral nor enteral nutrition can meet 50% of the protein and caloric requirements for more than 7 d, parenteral nutrition should be considered[135]. Routine gastric tube placement is not common in liver cancer surgery. If there are special circumstances that require gastric tube placement, it is recommended to remove it before the patient regains consciousness from anesthesia[136]. Therefore, postoperative nutritional support for liver cancer patients primarily consists of oral nutrition and daily meals.

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## CONCLUSION

The incidence and mortality rates of liver cancer are indeed considerably high, and currently, surgical resection is the primary modality of treatment. However, it is widely observed that liver cancer patients commonly experience malnutrition, leading to compromised immune function and an increased incidence of postoperative complications. Detecting early signs of nutritional deficiencies or potential issues in liver cancer patients and analyzing the underlying causes of malnutrition can be guided by the recommended tri-level nutritional diagnosis model proposed by the Chinese Society of Oncology Nutrition. Malnutrition in liver cancer primarily manifests as inadequate energy and protein intake. Consequently, nutritional support should primarily focus on energy and protein, while also ensuring the supplementation of other essential nutrients. Since the majority of liver cancer patients possess intact gastrointestinal tracts and unimpaired functionality, the primary mode of nutritional support is oral nutrient supplementation. In cases where some liver cancer patients or those in advanced stages experience digestive symptoms such as abdominal distension, which hinder oral nutrient intake, a combination of partial oral and enteral nutrition support can be considered. To evaluate the effectiveness of nutritional support, regular weekly nutritional reassessment should be conducted to gain insights into the patient's nutritional status. Therefore, it is recommended to involve a multidisciplinary team of nutrition management throughout the perioperative period, comprising professionals such as dietitians, pharmacists, physicians, nurses, psychotherapists, and rehabilitation therapists. Such a team can collaboratively develop and implement personalized nutritional support plans, monitor patients' nutritional status, and make necessary adjustments as required. Through comprehensive management and intervention, it is possible to improve the nutritional status of liver cancer patients, enhance the success rate of surgical procedures, and facilitate postoperative recovery. Certainly, this study still has its limitations. The viewpoints presented herein are derived from the synthesis and summarization of literature search findings. Incorporating specific case studies from the authors' institution could further substantiate the arguments

presented in this paper. Regrettably, due to the nature of this manuscript being a review article, such content was not included. Nevertheless, we believe that this article will serve as a valuable reference for advancing the nutritional management during the perioperative phase of liver cancer, contributing to the amelioration of patients' nutritional status and treatment outcomes.

## FOOTNOTES

**Author contributions:** Li XQ was responsible for the study concept and manuscript preparation; Liang Y and Huang CF was responsible for the intellectual content and manuscript review; Li SN, Cheng L, and You C were involved in the literature search and manuscript editing; Liu YX and Wang T performed the role of guarantor for the integrity and study design of the study; All authors have read and approved this article. Wang T and Liu YX, as co-corresponding authors, played an indispensable role in the conception, design, and writing of the manuscript, and provided financial support for it. Liu YX assisted and was responsible for re-analyzing and re-interpreting the data, creating figures, and conducting comprehensive literature searches. Wang T supervised the entire process of the project, as well as the preparation and submission of the current version of the manuscript. The collaboration between Wang T and Liu YX is crucial for the publication of this manuscript.

**Supported by** National Natural Science Foundation of China, No 81701888; Science and Technology Program of Sichuan Province, No. 2023YF50206; and Scientific Research Project of Sichuan Cadre Health Committee, No. 2022-211.

**Conflict-of-interest statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Country of origin:** China

**ORCID number:** Xiao-Qin Li 0009-0006-3552-5722; Tao Wang 0000-0003-1639-5361.

**Corresponding Author's Membership in Professional Societies:** The Health Management Committee of the Chinese Association of Rehabilitation Medicine, 060808268; The Children's Hospital Branch of the Chinese Hospital Association, 90376565; Vice Chairman of the Genetic, Metabolic, Endocrinology and Rare Disease Prevention and Control Branch of Sichuan Preventive Medicine Association, 20240179.

**S-Editor:** Li L

**L-Editor:** Filipodia

**P-Editor:** Zheng XM

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