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ORIGINAL RESEARCH

# Assessment of the Risk of Malnutrition or Frailty Among Patients Undergoing Liver Transplantation: A Hospital-Based Prospective Study

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**Objective:** We aimed to explore the status of nutritional and frailty in patients undergoing liver transplantation and the associated influencing factors.

**Methods:** We conducted a follow-up analysis of 44 patients who underwent liver transplantation between 2021 and 2022. We followed up and recorded the nutritional status and risk of weakness at different time-points (days 1, 2, 3, 6, 9, and 12) postoperatively. Patient information regarding demographics, physical examination, medical history, and perioperative blood tests were collected. Binary logistic regression was applied to identify risk factors for weakness after liver transplantation.

**Results:** The cohort comprised 44 liver transplant recipients, with a mean age of 47.66 years (standard deviation=9.49 years). Initial analysis revealed that, compared to the group without nutritional risks, the group with nutritional risks displayed elevated age and preoperative blood ammonia levels one week post-surgery. Moreover, this group had reduced levels of albumin and total bile acid preoperatively. Patients with preoperative nutritional risks were also prone to similar risks 2 weeks postoperatively. Further, a correlation was observed between preoperative pulmonary infections and increased frailty risk 6 days postoperatively. At both 9 and 12 days postoperatively, patients with frailty risk exhibited higher preoperative white blood cell counts and ammonia levels than those without. Multivariable analysis, controlling for confounding factors, indicated a significant association between preoperative nutritional status and nutritional risk 2 weeks postoperatively, as well as a link between preoperative white blood cell count and frailty risk at 12 days postoperatively.

**Conclusion:** There was a significant correlation between preoperative nutritional status and nutritional risk 2 weeks after liver transplantation, and preoperative white blood cell count was an independent risk factor for weakness 12 days postoperatively. Preoperative nutritional management for patients could potentially mitigate the likelihood of adverse clinical outcomes.

**Keywords:** malnutrition, frailty, liver transplantation, risk factors, epidemiology

## Introduction

In 2016, hepatic conditions, particularly cirrhosis and advanced liver disease, were among the top ten causes of male mortality in the United States (US).[1] Globally, liver diseases pose a critical public health challenge due to their extensive prevalence and typically adverse long-term health outcomes, contributing to approximately two million deaths annually; half from cirrhosis complications and the other half from viral hepatitis or liver cancer.[2] Cirrhosis ranks prominently in global health metrics, significantly contributing to disability-adjusted life years and mortality.[3] For individuals with terminal liver disease, liver transplantation remains the most effective treatment and, often, their sole chance for survival.[4]

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Protein-energy malnutrition, prevalent in patients awaiting liver transplantation, significantly impacts posttransplant morbidity and mortality.[5] Recent research has increasingly focused on frailty, which encompasses various aspects of health such as mobility, strength, and cognitive function, and is an important prognostic factor in liver disease management and transplantation processes.[6,7] Nutritional assessments in this context are guided by recommendations from the European Society of Parenteral and Enteral Nutrition, which endorses methods like the Subjective Global Assessment and bedside anthropometric measurements.[8] US experts have proposed a comprehensive approach to frailty assessment, including tools like the Karnofsky index and 6-minute walk test.[9] Moreover, Lai et al reported a novel liver-specific frailty index; it includes three simple, performance-based tests of physical frailty — grip strength, chair stands, and balance testing. This can objectively evaluate the frailty phenotype in patients with end-stage liver disease in the outpatient setting.[10] Despite these developments, the evaluation of nutritional status and frailty in liver transplant recipients is hindered by a lack of universally accepted and clinically practical assessment tools.[11]

Therefore, this study sought to elucidate the risks and contributing factors related to nutrition and frailty following liver transplantation.

# Methods

## Research Design and Participant Recruitment

This study, conducted from January to December 2022, involved patients who underwent liver transplantation at Shenzhen Third People's Hospital. Eligible participants included those with liver failure of various etiologies (such as posthepatitis B cirrhosis and alcoholic cirrhosis), undergoing their initial liver transplantation, aged ≥18 years, and without any mental or cognitive impairments. We excluded individuals with nonhepatogenic nutritional abnormalities, immune, or coagulation functions, as well as those with consciousness or severe cognitive issues, or inability to participate fully. Informed consent was secured from all participants, and the study's protocol received approval from the Medical Ethics Committee of Shenzhen Third People's Hospital, in line with the principles of the Declaration of Helsinki.

## Information Collection

The patient's admission time for transplantation surgery was taken as the baseline, and information on the day of admission, including demographic information, physical examination, and laboratory examination, was collected as pretransplant data. Demographic information (including age, age groups, education level, type of medical insurance, marital status) and personal medical history (including diabetes mellitus, hypertension, tumors, pulmonary infection, biliary complications, bleeding, rejection, deep vein thrombosis, wound infection, poor healing, etc.) were collected using standardized questionnaires.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), vital signs on the day before operation (including white blood cell (WBC), red blood cell (RBC), platelet (PLT), albumin (Alb), total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, blood ammonia and blood glucose level) and body mass index (BMI) were recorded during physical examinations. Overweightedness was defined as with BMI between 24.0 and 28.0 kg/m$^2$, and obesity was defined as with BMI ≥28.0 kg/m$^2$, according to the Coorperative Meta-analysis Group of China Obesity Task Force.[11]

## Evaluation of Nutrition and Frailty

In this study, frail mainly refers to physical weakness, which was evaluated according to the "fatigue, resistance, ambulation, illnesses, and loss of weight" (FRAIL) scale, which includes: (1) feelings of fatigue in the past 4 weeks; (2) a sense of resistance, with difficulty going up a flight of stairs; (3) decreased free activity, with inability to walk 100 m or 1 block; (4) coexistence of ≥5 diseases; and (5) body mass reduction, with a body mass decline of >3 kg in the past 6 months (not related to diet or exercise). A total score of 0 indicates no frailty, 1–2 indicates prefrailty, and 3–5 indicates frailty.[12]

The Nutritional Risk Screening Form (NRS2002) is a routine nutrition screening scale used in our hospital. It is applicable to individuals aged 18–90 years old, hospitalized for more than 1 day, and mental state. A total nutritional risk score of ≥3 indicates nutritional risk, and nutritional support treatment plan should be formulated according to the clinical status of patients. A score of ≤3 points indicates no nutritional risk at present, and nutritional risk screening should be reviewed a week later.

The disease severity was adjudged as follows. (1) Mild: patients with chronic diseases are hospitalized due to complications; the patient is weak but not bedridden, and the protein requirement is slightly increased, but can be compensated by oral administration and supplementation. (2) Moderate: patients need to stay in bed, such as major surgery; the protein requirements is increased, but most people can be restored by artificial nutrition. (3) Severe: patients on mechanical ventilation support in intensive care unit; protein requirements is increased and cannot be made up for by parenteral or enteral nutrition support, but such nutritional support can reduce the protein decomposition and nitrogen loss significantly.

Nutritional and frailty risk assessments and laboratory tests were performed one day. Nutritional risk assessments were performed at one and two weeks, and frailty risk assessments were performed at 1, 2, 3, 6, 9, and 12 days post operation (Figure 1).

## Statistical Analysis

The sample size was calculated according to the prevalence rate of postoperative frailty (0.6), difference between preoperative and postoperative prevalence (0.3), significance level (0.05), and statistical efficacy (0.8); the calculated sample size was 39.3 cases. Finally, a sample size of 44 cases was decided upon after considering a 10% dropout rate. We segregated participants into groups based on their nutritional and frailty statuses at various intervals. Continuous variables were analyzed via Student's *t*-test or Mann–Whitney *U*-test, and categorical data through the Chi-squared test. Categorical variables such as nutritional risk and frailty risk were compared by multiple sample rates, chi-square test, and pairwise comparison at different time points before and after the surgery. The statistical significance level of pairwise comparison was $P<0.007$. Logistic regression analysis was performed to find the factors associated with nutritional risk or frailty risk by using the variables with statistical significance in the univariate analysis. The association of nutritional risk or frailty risk with relevant factors was presented using relative risk (RR) and 95% confidence interval (CI). All significance tests were two-sided, and statistical significance was defined as $P<0.05$. SPSS version 25.0 for Windows (IBM Corp., Armonk, NY, USA) was used for the analyses.

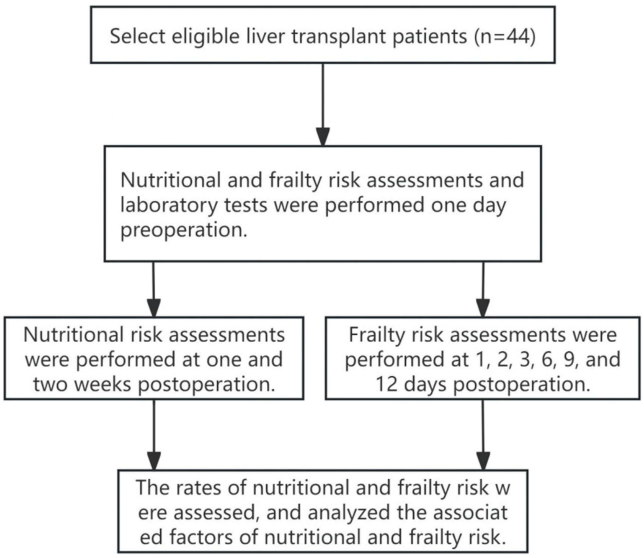


**Figure 1** Flow chat of the assessment of nutritional and frailty risk. The nutritional and frailty risk assessments and laboratory tests were performed one day. Nutritional risk assessments were performed at one and two weeks, and frailty risk assessments were performed at 1, 2, 3, 6, 9, and 12 days post operation.

# Result

## Demographic Characteristics

Overall, 44 patients who underwent liver transplantation were recruited in this study. In total, the average age of the participants was 47.66 years, and the majority of the population (68.2%) was 40–59 years old. Regarding the types of medical insurance, the study population mainly utilized employee medical insurance and urban residents medical insurance. Three-quarters of the patients undergoing liver transplantation had hepatitis B; the other common comorbidities were deep vein thrombosis (22.7%), pulmonary infection (18.2%), rejection (15.9%), and poor wound healing (15.9%). The average BMI of the participants was 23.25 kg/m$^2$; among them, the low body weight, normal body weight, overweight, and obesity groups accounted for 15.4%, 38.5%, 28.2% and 17.9%, respectively (Table 1).

## Nutrition or Frailty Risk

There were 70.5% and 43.9% patients with nutritional risk at 1 week and 2 weeks after the operation, respectively. The prevalence of nutritional risk at 1 week was significant higher than that at 2 weeks (P=0.013). The proportion of patients

**Table 1** Baseline Characteristic

| Factors | Men | Women | Total |
|---|---|---|---|
| Age, mean (SD), years | 47.23 (8.48) | 51.00 (16.40) | 47.66 (9.49) |
| Age group, n (%): | | | |
| <40 years | 8 (18.2) | 2 (4.5) | 10 (22.7) |
| 40 years~ | 29 (65.9) | 1 (2.3) | 30 (68.2) |
| ≥60 years | 2 (4.5) | 2 (4.5) | 4 (9.1) |
| Education, n (%): | | | |
| Primary school | 3 (6.8) | 0 | 3 (6.8) |
| Middle school | 9 (20.5) | 2 (4.5) | 11 (25.0) |
| High school | 11 (25.0) | 2 (4.5) | 13 (29.5) |
| University | 16 (36.4) | 1 (2.3) | 17 (38.6) |
| Medical Insurance Type, n (%): | | | |
| Employees | 21 (47.7) | 3 (6.8) | 24 (54.5) |
| Residents | 17 (38.6) | 0 | 17 (38.6) |
| Commercial insurance | 1 (2.3) | 1 (2.3) | 2 (4.5) |
| Self-pay | 0 | 1 (2.3) | 1 (2.3) |
| Marital Status, n (%): | | | |
| Unmarried | 6 (13.6) | 0 | 6 (13.6) |
| Married | 33 (75.0) | 5 (11.4) | 38 (86.4) |
| Complications, cases (%): | | | |
| Hepatitis B | 30 (68.2) | 3 (6.8) | 33 (75.0) |
| Hypertension | 2 (4.5) | 1 (2.3) | 3 (6.8) |
| Diabetes | 4 (9.1) | 1 (2.3) | 5 (11.4) |
| Tumour | 3 (6.8) | 0 | 3 (6.8) |
| Pulmonary infection | 6 (13.6) | 2 (4.5) | 8 (18.2) |
| Biliary complications | 1 (2.3) | 2 (4.5) | 3 (6.8) |
| Bleeding | 2 (4.5) | 0 | 2 (4.5) |
| Rejection Reaction | 6 (13.6) | 1 (2.3) | 7 (15.9) |
| Deep vein thrombosis | 9 (20.5) | 1 (2.3) | 10 (22.7) |
| Wound infection | 0 | 1 (2.3) | 1 (2.3) |
| Poor healing | 6 (13.6) | 1 (2.3) | 7 (15.9) |
| BMI, means (SD), kg/m$^2$ | 23.93 (6.11) | 17.32 (1.86) | 23.25 (6.14) |
| BMI groups, n (%): | | | |
| Low weight | 3 (7.7) | 3 (7.7) | 6 (15.4) |
| Normal weight | 14 (35.9) | 1 (2.6) | 15 (38.5) |
| Over weight | 11 (28.2) | 0 | 11 (28.2) |
| Obesity | 7 (17.9) | 0 | 7 (17.9) |

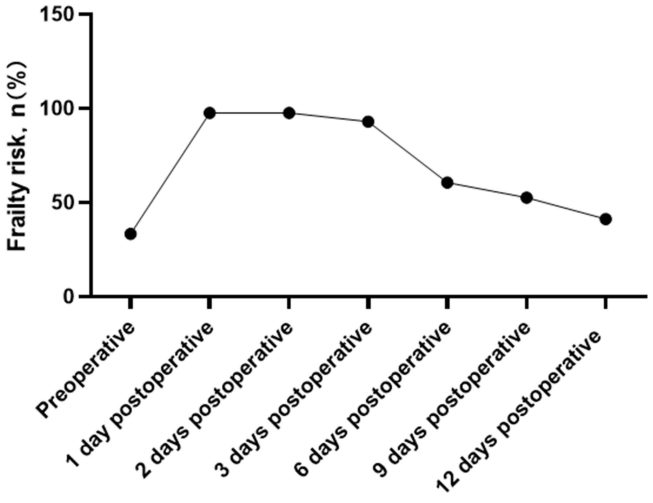


**Figure 2** Frequency of frailty risk at different time-points. The proportion of patients with frailty risk preoperatively and 1, 2, 3, 6, 9, and 12 days postoperatively were 33.3%, 97.6%, 97.6%, 92.9%, 60.5%, 52.5% and 41.2% respectively. There were significant statistical differences between the frequencies of frailty risk at different time-points (P<0.001; Figure 2).

with frailty risk preoperatively and 1, 2, 3, 6, 9, and 12 days postoperatively were 33.3%, 97.6%, 97.6%, 92.9%, 60.5%, 52.5% and 41.2% respectively. There were significant statistical differences between the frequencies of frailty risk at different time-points (P<0.001; Figure 2).

Additionally, the pairwise comparison results showed that the prevalence of frailty on days 1, 2, and 3 postoperatively was significantly higher than that on 1 day preoperatively (all P<0.001), and recovered to the preoperative level on day 6 after surgery (P<0.007).

## Univariate Analysis of the Risk of Nutritional and Frailty at Different Time-Points

The nutritional risk was older and showed elevated blood ammonia levels 1 day preoperatively and 1 week post-operatively compared to the non-nutritional risk group (P<0.05; Supplementary Table 1). Meanwhile, the nutritional risk group showed lower Alb and TBA levels on the day before the operation (P<0.05). Patients with preoperative nutritional risk were more likely to be at nutritional risk 2 weeks postoperatively.

Patients with pulmonary infections were more likely to have a risk of frailty 6 days postoperatively (P<0.05; Supplementary Table 2). In the groups of 9 days and 12 days postoperatively, the WBC and blood ammonia levels on the day before operation were higher in the patients with a risk of frailty than in those without (all P<0.05).

## Multivariate Analysis of the Nutritional Risk and Frailty at Different Time-Points

In the groups 1 week after the operation, after adjustment for age, Alb and TBA levels on the day before the operation, there were no statistically significant association between age and Alb levels and nutritional risk (all P>0.05), but the nutritional risk decreased by 8% with every 1 mg/L increment of TBA level (odds ratio [OR]=0.992, 95% CI: 0.984–0.999; P=0.050). The preoperative nutritional risk was related to postoperative nutritional risk at 2 weeks (OR=8.40, 95% CI: 1.50–47.04; P=0.015). The nutritional risk at 2 weeks postoperative was 8.7-fold in patients with preoperative nutritional risk than that in patients without. The preoperative WBC level was associated with frailty risk at 12 days postoperatively (OR=1.249, 95% CI: 1.008–1.547; P=0.042). A one-unit elevation in WBC level resulted in 24.9% increment of the frailty risk at 12 days postoperatively (Table 2).

# Discussion

The purpose of this study was to explore the nutritional or frailty risk and their associated factors after liver transplantation. This study revealed that there were significant differences in age, educational level, and preoperative Alb, TBA, and blood ammonia levels between the nutritional risk and non-nutritional risk groups. The preoperative

**Table 2** Multivariate Analysis of the Nutritional Risk Factor

| Risk Factors | RR (95% CI) | P |
|---|---|---|
| Nutrition: | | |
| At 1 week postoperative: | | |
| Age | 1.018 (0.896, 0.157) | 0.779 |
| Preoperative Alb level | 0.712 (0.494, 1.026) | 0.069 |
| Preoperative TBA level | 0.992 (0.984, 0.999) | 0.050 |
| At 2 weeks postoperative: | | |
| Preoperative nutritional risk | 8.400 (1.500, 47.041) | 0.015 |
| Frailty: | | |
| 9 days postoperative: | | |
| WBC level preoperative | 1.203 (0.982, 1.473) | 0.074 |
| 12 days postoperative: | | |
| WBC level preoperative | 1.249 (1.008, 1.547) | 0.042 |

nutritional risk was related to postoperative nutritional risk at 2 weeks; patients with pulmonary infection were more likely to have a risk of frailty at 6 days postoperatively. In the groups of 9 and 12 days after the operation, the WBC and blood ammonia levels on the day before the operation were higher in patients with a risk of frailty than that in those without. Moreover, the WBC level on the day before the operation had a significantly correlation with frailty risk at 12 days postoperatively.

In line with previous literature, our findings corroborate that age is a crucial factor regarding the postoperative nutritional risk, aligning with studies highlighting the association of frailty with cognitive decline, muscle weakening, and inflammation.[13,14]

Our findings showed that preoperative nutritional risk is associated with postoperative nutritional risk after liver transplantation. The nutritional risk at 2 weeks postoperatively increased by 7.4-fold in patients with preoperative nutritional risk than that in those without. Consistent with the findings of this study, previous studies have shown that preexisting malnutrition is associated with nutritional status and prognosis in liver transplant patients. A review has shown that administering 1.2–1.5 times the basal energy expenditure of patients before liver transplantation improves postoperative outcomes for patients undergoing liver transplantation.[15] Merli et al reported that malnutrition is a risk factor for complications and death after liver transplantation.[16] The study by Hammad et al showed that even with good liver function, preoperative nutritional changes persist long after transplantation. This phenomenon may be related to the liver–brain–gut axis regulatory system, in which changes in the gut microbiota composition, metabolism, and intestinal permeability all affect liver structure and function.[17] Preexisting malnutrition, which may be mediated by the liver–brain–gut axis regulation system, may further cause nutritional metabolism disorders and poor prognosis after liver transplantation.[18]

There have been few previous clinical studies on bile acid levels and nutritional status after liver transplantation. High TBA levels were a protective factor for nutritional risk after liver transplantation in this study. Each one-unit increment in the TBA level resulted in a 0.8% decrease in the nutritional risk rate. As derivative molecules of cholesterol, bile acids play an important role in nutrient absorption, glucose homeostasis and energy regulation, and systemic immune homeostasis regulation. In addition, the gut–liver axis plays a key role in regulating the enterohepatic circulation of bile acids, the size of bile acid pool, and the composition of bile acids, which control the overgrowth of intestinal bacteria that metabolize bile acids to regulate host metabolism.[19] TBA may reduce the risk of malnutrition after liver transplantation, which may be related to its protective effect on the liver and its interaction with the enterohepatic axis.[20] However, there is scant experimental evidence available at present, and further research is needed to verify this.

Our study also found that preoperative WBC levels were associated with weakness after liver transplantation. A study from South Korea found a positive association between neutrophils and mortality 90 days after liver transplantation.[21] Langer et al showed that pathological neutrophil migration predicted adverse outcomes in hospitalized patients with cirrhosis.[22] Leukocytosis and excessive inflammatory response play an important role in decompensation of cirrhosis and

are associated with organ failure and death. High levels of WBCs represent higher levels of inflammation, which can cause damage to other organs such as the liver, and may be one of the reasons behind the association between WBCs and weakness after liver transplantation.[23,24]

The limitations of our study included its small sample size and the data being confined to a single hospital, potentially affecting the generalizability of the findings. Additionally, the lack of comprehensive data on perioperative medication therapy may have influenced the accuracy of our results. Finally, we assessed frailty with the 5-item FRAIL scale, but did not evaluate the muscle loss or grip strength; this may have affected the results. These factors will be considered in future research.

## Conclusion

This study showed a clear association between preoperative nutritional status and low TBA and nutritional risk 2 weeks after liver transplantation. Moreover, the preoperative WBC count was an independent risk factor for frailty 12 days postoperatively. These findings contribute to understanding the nutritional and frailty risks among patients undergoing liver transplantation, providing valuable insights for clinicians to detect and intervene early to reduce the risk of adverse clinical outcomes.

## Abbreviations

LT, liver transplantation; ESPEN, European Society of Parenteral and Enteral Nutrition; SGA, Subjective Global Assessment; ADL, Activities of Daily Living; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

## Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

All organs were donated voluntarily with written informed consent, and that this was conducted in accordance with the Declaration of Istanbul. All patients have signed consent for participating this study. The study protocol was approved by the Medical Ethics Committee of Shenzhen Third People's Hospital (contract number: 2022-037-02), and conformed to the Declaration of Helsinki. The written infirmed consent was provided by every patient.

## Author Contributions

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

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## Disclosure

The authors declare that they have no competing interests in this work.

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