Protein Intake (<1.0 g/kg) Is a Risk Factor for Malnutrition in Patients With Cirrhosis.

Jin Hwa Park  
Asan Medical Center

Minkoo Kang  
Hanyang University

Dae Won Jun  
Hanyang University

Mimi Kim  
Hanyang University

Bo-kyeong Kang (✉️ dr.bokyeong.kang@gmail.com)  
Hanyang University

Research Article

Keywords: Patients with cirrhosis, Protein Intake, sarcopenia

DOI: https://doi.org/10.21203/rs.3.rs-132585/v1

License: ☺️ ☝️ This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

Background and aims

The prevalence of malnutrition in patients with cirrhosis is considerably high. Protein intake is a well-known risk factor for malnutrition, but studies on adequate protein intake are very scarce. We investigated the prevalence of malnutrition and amount of adequate protein intake in patients with cirrhosis.

Methods

In total, 361 patients with cirrhosis were enrolled. Muscle quality and quantity were retrospectively assessed using the grip strength test and bioelectrical impedance analysis. Subjective global assessment (SGA) of malnutrition and dietary intake assessments were performed by a clinical dietician.

Results

The prevalence rates of sarcopenia, malnutrition assessed by SGA, and inadequate energy intake were 22.7%, 13.6%, and 27.5% respectively. The prevalence of malnutrition evaluated using any of the assessment methods was 46.3%, and no significant difference was observed according to liver disease etiology. The prevalence of malnutrition increased with the increasing disease severity and decreasing BMI. The prevalence of malnutrition was 64.4% in patients with protein intake <1.0 g/kg. Low protein intake, Child–Pugh C grade, older age, and low BMI were independent risk factors for malnutrition in multivariate analysis.

Conclusion

Protein intake below 1.0 g/kg is an independent risk factor for malnutrition in patients with cirrhosis.

Introduction

Malnutrition is one of the most common complications of cirrhosis and is associated with high mortality, high prevalence of infection, and portal hypertension-related complications, such as hepatic encephalopathy and ascites. Nutritional assessments and monitoring are essential for patients with cirrhosis, and several tools for evaluating malnutrition have been proposed. Several assessment tools are currently used to assess for malnutrition in patients with liver disease; previous studies have reported a wide range of variability in the prevalence rate of malnutrition, from 5–99%, depending on the assessment tools used.

Recently, the European Association for the Study of the Liver proposed practice guidelines on nutrition in chronic liver disease. Body mass index (BMI) and disease severity have been suggested as the most important risk factors for malnutrition, but the other risk factors are unknown. Decreased protein intake is also an important risk factor for malnutrition. The recommended daily protein intake in normal people is 0.83 g/kg, while that in chronic liver disease patients is 1.2–1.5 g/kg. Patients with
chronic liver disease are recommended to consume 1.5 times more protein than that consumed by normal individuals. Patients with chronic liver disease experience protein deficiency and have a high incidence of malnutrition due to the following reasons: reduced diet, indigestion, malabsorption (fat malabsorption, vitamin malabsorption, bacterial overgrowth, and portal hypertensive enteropathy), kidney-related diseases, and metabolic abnormalities.(14) The recommended protein intake is based on the minimum protein requirement to maintain the nitrogen balance. Therefore, patients with liver disease should consume 1.2–1.5 g/kg/day of protein. The protein intake should be 1.5 times higher than the usual intake to prevent sarcopenia, which can lead to worse clinical outcomes.(15) A cutoff protein value of 1.2–1.5 g/kg/day was reported in a previous study involving patients with cirrhosis who consumed a high-protein diet. The study also showed that patients with cirrhosis should consume up to 1.8 g/kg of protein.(16) However, a protein intake of 0.8 g/kg/day only is required to achieve nitrogen balance in patients with alcoholic liver cirrhosis (LC),(17) and there is a lack of accurate evidence to show that 1.5 times higher protein intake than the usual intake can achieve nitrogen balance. Moreover, studies on the status of protein intake and adequate protein intake in patients with chronic liver disease are limited. In previous studies, the protein intake in patients with chronic liver disease was 1.16–1.31 g/kg.(18–20) However, the number of studies targeting all patients with chronic liver disease is relatively small, and the number of studies reporting the appropriate protein intake according to the severity of liver disease and various causes is limited.

Hence, we aimed to investigate the prevalence of malnutrition using various methods. In addition, we aimed to compare the frequency of malnutrition according to SGA, sarcopenia, and dietary intake records and assess the agreement between these tools in the era of obesity.

**Methods**

**Study design**

This study retrospectively evaluated 361 patients with cirrhosis who visited Hanyang University Hospital liver clinic between April 2018 and January 2019. Of the 361 patients, 12 patients were excluded from the analysis due to communication difficulties, and 29 patients were excluded because they had comorbid chronic conditions, including thyroid disease, chronic obstructive pulmonary disease, kidney disease, and cancer other than liver cancer. Additionally, 11 patients with inadequate food diary data were excluded (Fig. 1) and a total of 309 patients were included as a result. The study was approved by the Institutional Review Board (IRB) of Hanyang University Hospital (IRB approval number: 2019-05-018-001), and the study was performed in accordance with the relevant guidelines. The requirement for obtaining an informed consent was waived by the IRB.

**Inclusion and exclusion criteria**

Patients aged ≥ 19 years with cirrhosis were included in the study. LC was diagnosed based on clinical judgment or the results of imaging studies. Patients were classified as having alcoholic LC, non-alcoholic
steatohepatitis (NASH-LC), or viral hepatitis (viral LC) according to the etiology of liver disease.

Patients with a history of medication usage and dietary interventions to control weight within the last 6 months, a comorbid chronic condition that may cause weight loss (thyroid disease, chronic obstructive pulmonary disease, or kidney disease), and malignancy other than liver cancer were excluded.

Quality and quantity of muscle mass

To diagnose sarcopenia, muscle mass was measured using bioelectrical impedance analysis (BIA) (Inbody 370; Inbody USA, Cerritos, CA, USA). Sarcopenia was defined as the volume of appendicular skeletal muscle (ASM) divided by height in meter squared (m$^2$). The cutoff values were 7.0 kg/m$^2$ for men and 5.7 kg/m$^2$ for women.\(^{(21)}\) Fat-free mass index (FFMI) was computed as the volume of fat-free mass (kg), measured using BIA, divided by height in meter squared (m$^2$). Handgrip tests were performed using a hand dynamometer (Jamar Hydraulic Hand Dynamometer; Asimow Engineering Co., Grass Valley, CA) while the patients were in the standing position with their shoulders in full extension. The test was performed three times using the dominant hand, and the highest score was used in the analysis. Based on the Asian Working Group of Sarcopenia guidelines, 26 kg and 18 kg were used as the cutoff values for men and women, respectively.\(^{(21)}\)

Subjective global assessment

A clinical dietician with > 5 years of clinical experience performed subjective global assessment (SGA) \(^{(22)}\) via a survey and physical examination. The patients were assessed for weight loss, volume of dietary intake, gastrointestinal symptoms, functional disorders and subcutaneous fat loss, muscle atrophy, edema, and ascites. The patients were categorized into three groups—well-nourished (SGA A), mild/moderately malnourished (SGA B), and severely malnourished (SGA C) groups.\(^{(22)}\) Patients categorized into the SGA B or C groups (SGA scores of $\geq 6$) were screened for malnutrition.

Definition and assessment of dietary intake

The nutritionist assessed the patients’ dietary intake using a food frequency questionnaire (FFQ) via a face-to-face interview. The nutrients obtained from various dietary sources were computed using CAN-Pro 4.0\(^{(14)}\) based on the data of the 6th Korea National Health and Nutrition Examination Survey (2013–2015).\(^{(15)}\) The estimated daily requirements were calculated using Schofield’s modification of the Harris–Benedict equation,\(^{(23, 24)}\) and patients were screened for malnutrition if their total daily caloric consumption was lower than the estimated daily requirement.

Definition of malnutrition

Patients with malnutrition were assessed for undernutrition using one of the following screening methods: diagnosing sarcopenia, use of nutritional assessment tools, or use of dietary intake journals.\(^{(8)}\) According to the European Society for Clinical Nutrition and Metabolism guidelines, malnutrition is defined as BMI $< 18.5\ \text{kg/m}^2$; unintentional weight loss exceeding 10% regardless of the time or weight
loss of 5% within 3 months in addition to BMI < 20 kg/m² for individuals aged < 70 years and a BMI of 22 kg/m² for individuals aged ≥ 70 years; or FFMI < 15 for women and < 17 for men.(5)

**Statistical analysis**

Data analysis was performed using SPSS for Windows (Version 24; SPSS Inc., Chicago). All measurements are expressed as mean ± standard deviation. Analysis of variance, Student’s t-tests, and chi-square tests were used to examine the differences among groups, and a P-value of < 0.05 was considered significant. Additionally, Cohen's kappa analysis was performed to examine the level of agreement of malnutrition determined using the different malnutrition assessment methods. This study was a descriptive study based on multiple patient charts and did not include calculation of the sample size. All patients with cirrhosis who visited the outpatient department during the study period were enrolled.

**Results**

**Basic characteristics and prevalence of malnutrition**

A total of 309 patients with cirrhosis were included in the analyses. The mean patient age was 58.7 years, and 61.8% patients were men. In total, 88, 33, 172, 16 patients were categorized into the alcoholic LC, NASH-LC, viral LC, and other LC groups, respectively. The prevalence of sarcopenia was 22.7% (70/309). The prevalence of malnutrition according to SGA was 11.7% (36/309), and the prevalence of inadequate dietary intake was 27.5% (85/309). Approximately 46.3% (n = 143) patients satisfied one of the three definitions of malnutrition (Table 1).
| Characteristics                  | Total LC (n = 309) | Alcoholic LC (n = 88) | NASH-LC (n = 33) | Viral LC (n = 172) | Other LC (n = 16) | P     |
|---------------------------------|-------------------|----------------------|------------------|-------------------|------------------|-------|
| **Age (yr)**                    | 58.7 ± 9.26       | 56.7 ± 8.94          | 63.4 ± 9.31      | 58.5 ± 9.34       | 59.3 ± 6.78      | 0.005 |
| **Sex (%)**                     |                   |                      |                  |                   |                  |       |
| Male                            | 191 (61.8)        | 82 (93.2)            | 12 (36.4)        | 93 (54.1)         | 4 (25.0)         | < 0.001 |
| Female                          | 118 (38.2)        | 6 (6.8)              | 21 (63.6)        | 79 (45.9)         | 12 (75.0)        |       |
| **Height (cm)**                 | 164.5 ± 8.63      | 168.3 ± 6.66         | 161.4 ± 8.33     | 164.0 ± 8.84      | 156.5 ± 7.32     | < 0.001 |
| **Weight (kg)**                 | 66.6 ± 12.12      | 68.0 ± 12.80         | 63.7 ± 10.53     | 66.9 ± 12.25      | 61.5 ± 8.28      | 0.119 |
| **BMI (%)**                     |                   |                      |                  |                   |                  | 0.303 |
| < 18.5 (kg/m²)                  | 10 (3.3)          | 4 (4.8)              | 1 (3.0)          | 5 (2.9)           | 0 (0)            |       |
| 18.5–25 (kg/m²)                 | 165 (54.5)        | 52 (61.9)            | 18 (54.6)        | 85 (50.0)         | 10 (62.5)        |       |
| ≥ 25 (kg/m²)                    | 128 (42.2)        | 28 (33.3)            | 14 (42.4)        | 80 (47.1)         | 6 (37.5)         |       |
| **ASM (kg)**                    | 20.1 ± 4.79       | 22.4 ± 4.19          | 18.2 ± 4.72      | 19.7 ± 4.77       | 16.3 ± 2.37      | < 0.001 |
| **Percent body fat (%)**        | 28.0 ± 9.12       | 21.8 ± 8.61          | 31.1 ± 8.37      | 29.8 ± 8.17       | 34.4 ± 6.59      | < 0.001 |
| **FFMI (kg/m²)**                | 17.5 ± 2.41       | 18.6 ± 2.37          | 16.7 ± 2.31      | 17.2 ± 2.36       | 16.4 ± 1.59      | < 0.001 |
| **Handgrip strength (kg)**      | 30.0 ± 9.89       | 33.6 ± 7.75          | 23.9 ± 8.03      | 29.7 ± 10.68      | 25.1 ± 7.30      | < 0.001 |
| **Sarcopenia (%)**              | 70 (22.7)         | 16 (18.2)            | 9 (27.3)         | 41 (23.8)         | 4 (25.0)         | 0.339 |
| **Child–Pugh (%)**              |                   |                      |                  |                   |                  | 0.005 |

Data are expressed as mean ± standard deviation (number, %) Alcoholic LC, alcoholic liver cirrhosis; NASH-LC, nonalcoholic steatohepatitis-related liver cirrhosis; viral LC, viral liver cirrhosis; BMI, body mass index; ASM, appendicular skeletal muscle; FFMI, fat-free mass index; MELD, model for end-stage liver disease; SGA, subjective global assessment; EASL CPG, European Association for the Study of the Liver Clinical Practice Guidelines; ESPEN CPG, European Society for Parenteral and Enteral Nutrition Clinical Practice Guidelines
| Characteristics | Total LC (n = 309) | Alcoholic LC (n = 88) | NASH-LC (n = 33) | Viral LC (n = 172) | Other LC (n = 16) | P     |
|-----------------|-------------------|----------------------|------------------|---------------------|------------------|-------|
| A               | 266 (86.1)        | 66 (75.0)            | 30 (90.9)        | 155 (90.1)          | 15 (93.8)        |       |
| B               | 29 (9.4)          | 14 (15.9)            | 2 (6.1)          | 12 (7.0)            | 1 (6.2)          |       |
| C               | 14 (4.5)          | 8 (9.1)              | 1 (3.0)          | 5 (2.9)             | 0 (0)            |       |
| MELD score      | 8.6 ± 2.72        | 9.8 ± 3.78           | 8.2 ± 2.82       | 8.2 ± 1.84          | 7.28 ± 1.05      | < 0.001 |
| SGA (%)         | 0.186             |                      |                  |                     |                  |       |
| Total energy (kcal) | 2090 ± 910       | 2294 ± 940           | 2069 ± 962       | 2014 ± 895          | 1821 ± 632       | 0.114 |
| Inadequate (%)  | 85 (27.5)         | 22 (27.2)            | 9 (32.1)         | 49 (30.6)           | 5 (35.7)         | 0.894 |
| Carbohydrate (g)| 310 ± 126         | 316 ± 131            | 310 ± 130        | 281 ± 99            | 0.843            |       |
| Protein (g)     | 86 ± 46           | 100 ± 51             | 87 ± 48          | 74 ± 39             | 0.024            |       |
| Lipid (g)       | 57 ± 35           | 66 ± 38              | 57 ± 37          | 48 ± 29             | 0.038            |       |
| Cholesterol     | 417 ± 277         | 417 ± 316            | 438 ± 246        | 520 ± 480           | 0.448            |       |
| Vitamin A (µg)  | 984 ± 562         | 954 ± 596            | 1023 ± 575       | 1254 ± 986          | 0.264            |       |
| Vitamin C (mg)  | 145 ± 94          | 151 ± 113            | 130 ± 74         | 187 ± 124           | 0.243            |       |
| Vitamin D (µg)  | 5.0 ± 4.47        | 4.7 ± 3.77           | 6.4 ± 7.15       | 7.4 ± 7.74          | 0.040            |       |
| Vitamin E (mg)  | 18.2 ± 10.46      | 17.2 ± 9.78          | 20.1 ± 11.03     | 24.5 ± 17.85        | 0.058            |       |
| Thiamin (mg)    | 1.6 ± 0.84        | 1.5 ± 0.79           | 1.9 ± 1.10       | 1.9 ± 1.14          | 0.113            |       |
| Riboflavin (mg) | 1.4 ± 0.78        | 1.4 ± 0.77           | 1.6 ± 0.88       | 1.9 ± 1.38          | 0.088            |       |

Data are expressed as mean ± standard deviation (number, %) Alcoholic LC, alcoholic liver cirrhosis; NASH-LC, nonalcoholic steatohepatitis-related liver cirrhosis; viral LC, viral liver cirrhosis; BMI, body mass index; ASM, appendicular skeletal muscle; FFMI, fat-free mass index; MELD, model for end-stage liver disease; SGA, subjective global assessment; EASL CPG, European Association for the Study of the Liver Clinical Practice Guidelines; ESPEN CPG, European Society for Parenteral and Enteral Nutrition Clinical Practice Guidelines
Prevalence of malnutrition according to etiology

In total, 39 (44.3%) patients in the alcoholic LC group, 16 (48.5%) patients in the NASH-LC group, 80 (46.5%) patients in viral LC group, and 8 (50.0%) patients in the other LC group satisfied one of the three definitions of malnutrition (Table 1, Fig. 2). Although the prevalence of decompensated cirrhosis (Child–Pugh B and C grades) and the model for end-stage liver disease (MELD) scores were higher in the alcoholic LC group than in the viral LC and NASH-LC groups (P = 0.005 and P < 0.001, respectively), the prevalence of malnutrition was not significantly different among these groups (P = 0.962; Table 1). The prevalence of sarcopenia, inadequate dietary intake, and SGA malnutrition was not significantly different according to the etiology of cirrhosis. Although the total energy intake was similar across the etiology-based groups, the alcoholic LC group had the highest protein and fat consumption. Lipid intake was higher in the alcoholic LC and NASH-LC groups. None of the groups showed other between-group differences in dietary intake.

Prevalence of malnutrition according to disease severity

In total, 266 (88.1%) patients were classified as having Child–Pugh grade A, while 43 (13.9%) patients were classified as having Child–Pugh grade B or C. A total of 117 (44.0%) in the Child–Pugh A group, 15 (51.7%) in the Child–Pugh B group, and 11 (78.6%) in the Child–Pugh C group satisfied one of the three definitions of malnutrition. The prevalence of malnutrition significantly increased with the increasing disease severity (P = 0.034; Table 2).
Table 2
Clinical parameters of malnutrition in patients classified based on liver function and body mass index

| Characteristics | Child–Pugh classification | Body mass index (kg/m²) |
|----------------|---------------------------|------------------------|
|                | A (n = 266)               | B (n = 29)             | C (n = 14)   | P (n = 10) | 18.5–25 (n = 165) | ≥ 25 (n = 128) |
| BMI (%, kg/m²) |                           |                        |              |           |                 |               |
| < 18.5         | 8 (3.1)                   | 0 (0.0)                | 2 (14.3)     |           |                 |               |
| 18.5–25        | 144 (55.4)                | 15 (51.7)              | 6 (42.8)     |           |                 |               |
| ≥ 25           | 108 (41.5)                | 14 (48.3)              | 6 (42.8)     |           |                 |               |
| Child–Pugh classification (%) | 8 (80.0) | 144 (87.3) | 108 (79.5) | 0.145     |                 |               |
| A              |                           |                        |              |           |                 |               |
| B              |                           |                        |              |           |                 |               |
| C              | 2 (20.0)                  | 6 (3.3)                | 6 (6.8)      |           |                 |               |
| ASM (kg)       | 20 ± 4.7                  | 21 ± 4.4               | 23 ± 5.8     | 0.041     | 16 ± 3.6        | 19 ± 4.4      | 22 ± 4.9      | < 0.001 |
| FFMI (kg/m²)   | 17 ± 2.3                  | 21 ± 4.5               | 23 ± 5.8     | < 0.001   | 14 ± 1.7        | 17 ± 2.0      | 19 ± 2.3      | < 0.001 |
| Handgrip strength (kg) | 30 ± 10.2 | 31 ± 8.3 | 28 ± 4.8 | 0.637 | 23 ± 6.0 | 29 ± 9.9 | 32 ± 9.6 | 0.006 |
| Sarcopenia (%) | 58 (21.8)                 | 6 (20.7)               | 6 (42.9)     | 0.160     | 8 (80.0)        | 49 (29.7)     | 13 (10.2)     | < 0.001 |
| SGA (%)        | 58 (21.8)                 | 6 (20.7)               | 6 (42.9)     | 0.160     | 8 (80.0)        | 49 (29.7)     | 13 (10.2)     | < 0.001 |

Data are expressed as mean ± standard deviation (number, %). BMI, body mass index; ASM, appendicular skeletal muscle mass; FFMI, fat-free mass index; SGA, subjective global assessment;

EASL CPG, European Association for the Study of the Liver Clinical Practice Guidelines; ESPEN CPG, European Society for Parenteral and Enteral Nutrition Clinical Practice Guidelines
## Child–Pugh classification

| Type | 24 (9.2) | 3 (10.7) | 7 (50.0) |
|------|----------|----------|----------|

## Body mass index (kg/m\(^2\))

| Type | 4 (40.0) | 18 (10.9) | 11 (8.9) |
|------|----------|------------|----------|

## Dietary intake

|       | Mean ± SD | Mean ± SD | Mean ± SD | P-value |
|-------|-----------|-----------|-----------|---------|
| Total energy (kcal) | 2086 ± 900 | 2099 ± 969 | 2137 ± 1067 | 0.982 |
| Inadequate (%) | 68 (28.0) | 12 (44.4) | 5 (38.5) | 0.167 |
| Carbohydrate (g) | 309 ± 124 | 315 ± 120 | 335 ± 169 | 0.763 |
| Protein (g) | 86 ± 45 | 88 ± 58 | 84 ± 51 | 0.969 |
| Lipid (g) | 57 ± 34 | 57 ± 41 | 53 ± 33 | 0.939 |

## Malnutrition (%)

|       | ESPEN CPG | EASL CPG |
|-------|-----------|----------|
| Malnutrition (%) | 27 (10.5) | 117 (44.0) |
| by ESPEN CPG | 2 (6.9) | 15 (51.7) |
| by EASL CPG | 4 (28.6) | 11 (78.6) |

Data are expressed as mean ± standard deviation (number. %). BMI, body mass index; ASM, appendicular skeletal muscle mass; FFMI, fat-free mass index; SGA, subjective global assessment; ESPEN CPG, European Society for Parenteral and Enteral Nutrition Clinical Practice Guidelines; EASL CPG, European Association for the Study of the Liver Clinical Practice Guidelines

---

## Prevalence of malnutrition according to body mass index

In total, 9 (90.0%) patients in the BMI < 18.5 kg/m\(^2\) group, 81 (49.1%) patients in the BMI 18.5–25 kg/m\(^2\) group, and 52 (40.6%) patients in the BMI > 25 kg/m\(^2\) group satisfied one of the three definitions of malnutrition. The prevalence of malnutrition increased with the decreasing BMI, and the differences were statistically significant (P = 0.007; Table 2). The proportion of patients with sarcopenia and low SGA in the BMI < 18.5 kg/m\(^2\) group was 80% and 50%, respectively. The prevalence of sarcopenia increased with the decreasing BMI (P for trend < 0.001).

## Prevalence of malnutrition according to sarcopenia, SGA, and dietary intake
A total of 36 (13.6%), 70 (22.7%), and 85 (27.5%) patients had abnormal SGA, sarcopenia, and inadequate dietary intake, respectively (Table 3 and Fig. 4). The prevalence of malnutrition by SGA significantly increased with the decreasing BMI and increasing Child–Pugh score. Malnutrition according to sarcopenia was significantly associated with BMI, but it was not statistically associated with the cause or severity of the disease. The prevalence of energy malnutrition (inadequate dietary intake) was not associated with the cause and severity of the disease or BMI.

Table 3
Differences in liver function, body mass index, and etiology according to status of malnutrition

| Classification | Sarcopenia |  |  |  |  |
|----------------|------------|---|---|---|---|
|                | Presence (n = 70) | P | Presence (n = 36) | P | Presence (n = 85) | P | Presence (n = 143) | P |
| BMI (%) kg/m^2 | < 0.001    | 0.017 | 0.521 | 0.007 |
| < 18.5         | 8 (80.0)   | 7 (70.0) | 2 (20.0) | 9 (90.0) |
| 18.5–25        | 49 (29.7)  | 18 (10.9) | 44 (26.7) | 81 (49.1) |
| ≥ 25           | 13 (10.2)  | 11 (8.6) | 37 (28.9) | 52 (40.6) |
| Child–Pugh (%) | < 0.001    | 0.111 | 0.034 |
| A              | 58 (21.8)  | 25 (8.8) | 68 (25.6) | 117 (44.0) |
| B              | 6 (20.7)   | 4 (26.7) | 12 (41.4) | 15 (51.7) |
| C              | 6 (42.9)   | 7 (70.0) | 5 (35.7) | 11 (78.6) |
| Etiology (%)   | 0.339      | 0.055 | 0.510 | 0.962 |
| Alcohol        | 16 (18.2)  | 15 (17.0) | 22 (25.0) | 39 (44.3) |
| NASH           | 9 (27.3)   | 3 (9.1) | 9 (27.3) | 16 (48.5) |
| Viral          | 41 (23.8)  | 18 (10.5) | 49 (28.5) | 80 (46.5) |
| Others         | 4 (25.0)   | 0 (0.0) | 5 (31.3) | 8 (50.0) |

BMI, body mass index; SGA, subjective global assessment; NASH, nonalcoholic steatohepatitis; P < 0.05

Risk factors for malnutrition (multivariate analysis)

Logistic regression analysis was performed to identify the risk factors that affect the prevalence of malnutrition. The etiology of LC did not influence the prevalence of malnutrition. However, low protein intake (< 1.0 g/kg), Child–Pugh C grade, older age, and low BMI were independent risk factors for
malnutrition (Table 4). Among the patients with cirrhosis, 43.6% patients consumed < 1.0 g/kg of protein per day. The prevalence of malnutrition was 69.2% among patients with a protein intake of < 1.0 g/kg/day. Based on the receiver operating characteristic curve, protein intake showed the best performance in predicting malnutrition (Fig. 3). The areas under the curve for protein intake, BMI, and the MELD score were 0.788, 0.600, and 0.473, respectively.

| Table 4                                                                 |
|------------------------------------------------------------------------|
| Risk factors of malnutrition                                           |
| **Univariate**                                                        |
| **Multivariate**                                                       |
| **Exp(β)**                | **P**  | **Exp(β)**                | **P**  |
| Age                      | 1.03   | 0.009                      | 1.03   | 0.011             |
| BMI (kg/m²)               | 0.90   | 0.002                      | 0.84   | 0.002             |
| Etiology                  | 0.691  |                           | 0.657  |                   |
| Protein (g)               | 0.22   | < 0.001                    | 0.18   | < 0.001           |
| Child–Pugh classification  | 0.017  |                           | 0.031  |                   |

Data are expressed as P values and Exp(β). Exp(β), odds ratio confidence interval; BMI, body mass index; P < 0.05

**Discussion**

In this study, 46.3% patients had malnutrition. The prevalence rates of malnutrition were 78.6% and 64.4% among patients with Child–Pugh grade C and those with protein intake < 1.0 g/kg/day, respectively.

A previous study reported a protein intake of 1.16–1.31 g/kg/day in patients with liver disease, which is not significantly different from the 1.29 g/kg/day protein intake indicated in this study. In a previous study, the average patient age with compensated viral liver cirrhosis was 68.3 years, which was higher than that in this study (58.7 years). However, the mean patient age in this study was similar to that in other studies, and no significant difference was observed in terms of sex. Previous studies included non-cirrhotic Hepatitis C virus (HCV) patients, non-LC and LC patients, or viral LC patients. This study included all patients with chronic liver disease and analyzed and compared the nutritional intake according to the LC status and cause and severity of the disease. A 24-hour recall method, a food intake frequency recall method, a meal diary method, and an actual measurement method were used to determine the study participants’ nutrition intake. In most previous studies, protein intake was assessed using the 24-hour recall method. The recall method is used to estimate the nutrient intake from the surveyed data based on the type and amount of food consumed within 24 hours. It can be performed within a short period of time, and only slight changes in the dietary habits can occur; however, this method cannot be used to measure the food intake based on the 24-hour data, and a recall bias may potentially occur. The most accurate measurement method is the weighing method, which can accurately
measure the food intake by weighing the food ingredients cooked before meals and subtracting the amount of food remaining after the meal. However, this method is difficult to apply in the clinical setting. This study confirmed the nutrient intake in patients with chronic liver disease using the dietary diary method. The results of assessment using this method were not considered valid due to the limited food list. However, it had lesser recall bias and was a relatively accurate method as it was possible to record the type of food and food intake in a diary format while the participant was eating.

In this study, 13.6% patients with cirrhosis had malnutrition based on the SGA results. In previous studies, the prevalence of malnutrition varied from 5–99% according to the definition of malnutrition. (3, 9–11, 19, 25) In a previous study involving 1,402 patients published in 1994, mid-arm muscle circumference and mid-arm fat circumference were measured, and malnutrition was defined as a median value of < 5%. In this study, the prevalence of malnutrition was 30%. The prevalence of malnutrition was high in patients with Child–Pugh grades B and C, and no significant difference was observed between the two study groups according to the cause of cirrhosis. (11) Malnutrition was defined as protein-calorie malnutrition in 300 patients, and 38.3% malnutrition cases were reported in 2006. The prevalence of malnutrition also increased with the increasing disease severity, but malnutrition was not found to be related with the cause and prevalence of cirrhosis. (19) Other previous studies have used various evaluation methods. SGA, prognostic nutritional index, and handgrip strength were used to diagnose malnutrition in 50 patients in 2005, and 28%, 18.7%, and 63% of the patients who underwent the abovementioned tests, respectively, were reported to have malnutrition. (25) Another study diagnosed malnutrition according to handgrip strength, mid-arm muscle circumference, SGA, and corrected BMI and reported prevalence rates of 67%, 58%, 58%, and 5%. (3) However, no recent studies have used these evaluation methods in a large number of patients who showed an improvement in nutritional status compared with that before 2000. This study was conducted to evaluate the prevalence of malnutrition using the anthropometric method, SGA, and dietary intake in > 300 patients with cirrhosis.

It is unclear whether there is a difference in the prevalence of malnutrition according to the etiology of cirrhosis. Some studies showed a higher prevalence of malnutrition in patients with alcoholic cirrhosis than in those with non-alcoholic cirrhosis. (26, 27) However, a significant difference was found in the baseline severity of liver disease between the two patient groups and the assessment method used in these studies may not be optimal. For example, it might be inappropriate to measure the simple skin fold thickness and body fat mass of patients with NASH-associated cirrhosis to assess malnutrition. The total fat mass is relatively preserved in patients with NASH cirrhosis. In our study and previous studies, (3, 28) the prevalence of low SGA and sarcopenia did not differ according to etiology of the disease.

The present study has several limitations. First, sarcopenia was diagnosed by measuring the ASM using BIA, and the results could be influenced by excess body fluid. Although the proportion of patients with generalized edema and/or ascites was small, the prevalence of sarcopenia can be overestimated in patients with decompensated diseases. Assessment of the psoas muscle area using abdominal computed tomography, the phase angle \( \alpha \), or body cell mass, which is not affected by fluid accumulation, is more appropriate in patients with decompensated cirrhosis to evaluate the presence of sarcopenia. (29,
Second, the study included outpatients, and the number of patients with decompensated cirrhosis was relatively small. Hence, future studies should be conducted in a larger sample of patients with cirrhosis to assess their nutritional status and evaluate the prevalence of malnutrition in terms of the severity of cirrhosis. Third, nutrient intake assessments were performed using an FFQ. The volume of food intake is more accurately evaluated using a 3-day dietary journal, which includes the food intake during the weekend. Although the FFQ allows the examination of dietary habits in patients with chronic disease, it is difficult to accurately assess the volume of food intake using this method.

In conclusion, the prevalence of malnutrition, assessed using various assessments, was 46.3%. The prevalence of malnutrition increased as the disease severity increased and protein consumption decreased. The prevalence of malnutrition was extremely high in patients with a protein intake of < 1.0 g/kg. Taken together, the study suggests that protein intake is a good indicator of adequate dietary intake, and 39.5% patients with cirrhosis consume < 1.0 g/kg of protein.

**Declarations**

**Data availability statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Acknowledgements**

Financial support statement: This work was supported by the research fund from Hanyang University (HY-2018). The funding source had no role in the study design; implementation; data collection, analysis, and interpretation; or preparation, review, or approval of the manuscript.

**Authors’ contributions**

(I) Conception and design: Bo-kyeong Kang

(II) Administrative support: Research fund from Hanyang University (HY-2018)

(III) Provision of study materials or patients: Dae Won Jun

(IV) Collection and assembly of data: Minkoo Kang

(V) Data analysis and interpretation: Jin Hwa Park and Mimi Kim

(VI) Manuscript writing: Jin Hwa Park and Minkoo Kang

(VII) Final approval of manuscript: All authors

**Conflicts of interest**
The authors declare no competing interests.

References

1. Gunsar F, Raimondo ML, Jones S, Terreni N, Wong C, Patch D, et al. Nutritional status and prognosis in cirrhotic patients. Aliment Pharmacol Ther. 2006;24(4):563-72.
2. Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, et al. Nutrition and survival in patients with liver cirrhosis. Nutrition. 2001;17(6):445-50.
3. Huisman EJ, Trip EJ, Siersema PD, van Hoek B, van Erpecum KJ. Protein energy malnutrition predicts complications in liver cirrhosis. Eur J Gastroenterol Hepatol. 2011;23(11):982-9.
4. Merli M, Lucidi C, Giannelli V, Giusto M, Riggio O, Falcone M, et al. Cirrhotic patients are at risk for health care-associated bacterial infections. Clin Gastroenterol Hepatol. 2010;8(11):979-85.
5. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015;34(3):335-40.
6. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. JPEN J Parenter Enteral Nutr. 2010;34(2):156-9.
7. Amodio P, Bemeur C, Butterworth R, Cordoba J, Kato A, Montagnese S, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. Hepatology. 2013;58(1):325-36.
8. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol. 2019;70(1):172-93.
9. Figueiredo FA, Dickson ER, Pasha TM, Porayko MK, Therneau TM, Malinchoc M, et al. Utility of standard nutritional parameters in detecting body cell mass depletion in patients with end-stage liver disease. Liver Transpl. 2000;6(5):575-81.
10. Fernandes SA, Bassani L, Nunes FF, Aydos ME, Alves AV, Marroni CA. Nutritional assessment in patients with cirrhosis. Arq Gastroenterol. 2012;49(1):19-27.
11. Nutritional status in cirrhosis. Italian Multicentre Cooperative Project on Nutrition in Liver Cirrhosis. J Hepatol. 1994;21(3):317-25.
12. Eghtesad S, Poustchi H, Malekzadeh R. Malnutrition in liver cirrhosis: the influence of protein and sodium. Middle East J Dig Dis. 2013;5(2):65-75.
13. Baum JI, Kim IY, Wolfe RR. Protein Consumption and the Elderly: What Is the Optimal Level of Intake? Nutrients. 2016;8(6).
14. Juakiem W, Torres DM, Harrison SA. Nutrition in cirrhosis and chronic liver disease. Clin Liver Dis. 2014;18(1):179-90.
15. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol. 2016;65(6):1232-44.

16. Nielsen K, Kondrup J, Martinsen L, Dossing H, Larsson B, Stilling B, et al. Long-term oral refeeding of patients with cirrhosis of the liver. Br J Nutr. 1995;74(4):557-67.

17. Nielsen K, Kondrup J, Martinsen L, Stilling B, Wikman B. Nutritional assessment and adequacy of dietary intake in hospitalized patients with alcoholic liver cirrhosis. Br J Nutr. 1993;69(3):665-79.

18. Gottschall CB, Pereira TG, Rabito EI, Alvares-Da-Silva MR. Nutritional Status and Dietary Intake in Non-Cirrhotic Adult Chronic Hepatitis C Patients. Arq Gastroenterol. 2015;52(3):204-9.

19. Carvalho L, Parise ER. Evaluation of nutritional status of nonhospitalized patients with liver cirrhosis. Arq Gastroenterol. 2006;43(4):269-74.

20. Hayashi F, Momoki C, Yuikawa M, Simotani Y, Kawamura E, Hagihara A, et al. Nutritional status in relation to lifestyle in patients with compensated viral cirrhosis. World J Gastroenterol. 2012;18(40):5759-70.

21. Chen LK, Liu CK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc. 2014;15(2):95-101.

22. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr. 1987;11(1):8-13.

23. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39 Suppl 1:5-41.

24. Harris JA, Benedict FG. Biometric Studies of Basal Metabolism in Man. Publication No. 279. Washington, DC: Carnegie Institute of Washington. 1919:223-50.

25. Alvares-da-Silva MR, da Silveira TR. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. Nutrition. 2005;21(2):113-7.

26. Caly WR, Strauss E, Carrilho FJ, Laudanna AA. Different degrees of malnutrition and immunological alterations according to the aetiology of cirrhosis: a prospective and sequential study. Nutr J. 2003;2:10.

27. Maharshi S, Sharma BC, Srivastava S. Malnutrition in cirrhosis increases morbidity and mortality. J Gastroenterol Hepatol. 2015;30(10):1507-13.

28. Tandon P, Raman M, Mourtzakis M, Merli M. A Practical Approach to Nutritional Screening and Assessment in Cirrhosis. Hepatology. 2017;65(3):1044-57.

29. Selberg O, Selberg D. Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients, and patients with liver cirrhosis. Eur J Appl Physiol. 2002;86(6):509-16.

30. Pirlich M, Schutz T, Spachos T, Ertl S, Weiss ML, Lochs H, et al. Bioelectrical impedance analysis is a useful bedside technique to assess malnutrition in cirrhotic patients with and without ascites. Hepatology. 2000;32(6):1208-15.
Figure 3

Receiver operating characteristic curve of factors affecting malnutrition (A) Area under the curve of the factors affecting malnutrition based on the definition of malnutrition. (B) Area under the curve of factors affecting malnutrition based on sarcopenia. (C) Area under the curve of factors affecting malnutrition based on dietary intake. (D) Area under the curve of factors affecting malnutrition based on SGA.