Nutritional assessment tool for predicting sarcopenia in chronic liver disease

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Abstract

Background Subjective global assessment (SGA) and Royal Free Hospital-global assessment (RFH-GA) are clinically useful for assessing malnutrition. This study aimed to investigate the relationship between sarcopenia, which predicts poor clinical outcomes in patients with chronic liver disease (CLD), and these two methods.

Methods This retrospective study included 240 consecutive patients admitted to our hospital between October 2011 and January 2014. Sarcopenia and RFH-GA were evaluated using anthropometric measurements and computed tomography-based skeletal muscle area. The primary outcome was whether nutritional assessment methods could predict sarcopenia. In addition, factors associated with sarcopenia and mortality were evaluated.

Results The median age was 70 years, 67% were men, and 17% had sarcopenia. Malnourished patients assessed by SGA ($P = 0.02$) and RFH-GA ($P < 0.001$) had a significantly higher prevalence of sarcopenia than did well-nourished patients. After adjustment for age, sex, aetiology, and albumin, multivariate analysis revealed that RFH-GA, but not SGA, was a significant predictor of sarcopenia [odds ratio, 2.47; 95% confidence interval (CI), 1.15–5.33]. During a median follow-up of 2.7 years, 113 patients died. The overall survival rates were significantly lower in malnourished patients assessed by SGA ($P < 0.001$) and RFH-GA ($P < 0.001$) than in well-nourished patients. Multivariate analysis revealed that RFH-GA [hazard ratio (HR), 1.51; 95% CI, 1.02–2.23] and SGA (HR, 1.99; 95% CI, 1.19–3.32) were independently associated with mortality.

Conclusions Royal Free Hospital-global assessment is a simple bedside screening tool for identifying sarcopenia and predicting mortality in patients with CLD.

Keywords Malnutrition; Mortality; Nutrition; Subjective global assessment; Royal Free Hospital-global assessment

Introduction

Malnutrition is one of the most common complications of advanced chronic liver disease (CLD).1 Malnutrition is a multifactorial disease that emerges from various factors, including decreased dietary intake, malabsorption, and abnormal nutrient metabolism.1–3 The prevalence of malnutrition varies widely depending on the methods used for nutritional assessment and the degree of liver dysfunction.3 Poor nutritional status is associated with clinical deterioration, liver disease severity, and complications, such as infections, hepatic encephalopathy (HE), ascites, sarcopenia, and mortality, in patients with cirrhosis and in those listed for liver transplantation.3–6 Because malnutrition...
is a potentially modifiable condition by nutritional intervention, patients with CLD should receive a more detailed nutritional assessment to evaluate the presence and severity of malnutrition.6–8

Diagnosing malnutrition requires various nutritional measurements including body mass index (BMI), mid-arm muscle circumference (MAMC), subjective global assessment (SGA), Royal Free Hospital-global assessment (RFH-GA), and sarcopenia.6–8 In particular, sarcopenia is well reported to be a major component of malnutrition.9,10 Several factors predispose patients with CLD to sarcopenia. These factors include increased skeletal muscle ammonia, decreased testosterone and growth hormone, endotoxaemia, and reduced dietary intake, especially branched-chain amino acid reduction, all of which impair protein synthesis and contribute to sarcopenia.9,10 Sarcopenia has recently attracted considerable attention as it is associated with adverse clinical outcomes, including poor quality of life, HE, and mortality in patients with CLD.5,11–13 Diagnosing sarcopenia is thus clinically important to identify patients at risk of poor clinical outcomes.

Many studies on sarcopenia use cross-sectional computed tomography (CT) images to evaluate the skeletal muscle area at the third lumbar vertebral level.10 The potential advantage of using CT images is that it can accurately and objectively estimate muscle mass without the influence of fluid overload or ascites.10 However, the routine use of CT images seems to be clinically impractical due to its cost, radiation exposure, and the need for trained personnel.6 Additionally, muscle mass and nutritional status in patients with CLD change dynamically in their clinical course.24 Reliable nutritional assessment methods that can be repeatedly performed are thus required to trace dynamic changes in nutritional status.

Subjective global assessment is among the most widely used nutritional screening tools in various diseases owing to its simplicity and safety.15,16 SGA has also proven to be useful for the assessment of the nutritional status of patients with CLD.6,7 RFH-GA is a detailed nutritional assessment method that uses BMI, MAMC, and dietary intake.17 Several reports have demonstrated that RFH-GA can identify patients with advanced liver disease at risk of malnutrition.18

Although SGA and RFH-GA are beneficial for assessing nutritional status, identifying patients at high risk of malnutrition, and predicting clinical outcomes in patients with CLD, the relationship between sarcopenia and these two methods is still not yet fully understood. The primary aim of this study was to identify the relationship between sarcopenia and SGA and RFH-GA in patients with CLD. As a secondary aim, we investigated the prevalence of sarcopenia and malnutrition and explored the relationship between nutritional status and survival in these patients.

Methods

Study design and outcome

A total of 240 consecutive patients with CLD were retrospectively recruited for this study. The primary outcome was to clarify the relationship between sarcopenia and SGA and RFH-GA in patients with CLD. The secondary outcomes were to determine the prevalence of sarcopenia and malnutrition and to explore their association with death from all causes. Survival time was calculated as the time between entry and the last visit, date of death, or 30 November 2018, whichever occurred first.

Study patients and clinical data

The subjects were selected from patients with CLD who were admitted to the Gifu University Hospital (Gifu, Japan) between October 2011 and January 2014. The inclusion criteria were patients aged 20 years or older, CLD of any aetiology, and nutritional assessment including sarcopenia, SGA, and RFH-GA. Patients required CT images for the diagnosis of sarcopenia within 2 months of enrolment. Exclusion criteria included liver transplantation and other organ transplantations, active malignancies except for hepatocellular carcinoma (HCC), organ failure except for liver failure, and active infection.

Patients’ clinical characteristics and laboratory variables were collected from electronic medical records at the time of enrolment. Ascites and HCC were evaluated by medical imaging, such as CT images. HE was assessed by each physician according to the West Haven Criteria.19 The degree of liver dysfunction was estimated using model for end-stage liver disease (MELD) scores.6 Laboratory parameters were estimated using standard methods at the clinical laboratory of the Gifu University Hospital.

Assessment of sarcopenia

Sarcopenia was diagnosed according to the criteria proposed by the Japan Society of Hepatology, which was based on hand grip strength (HGS) and muscle mass.20 The HGS cut-off values to identify low muscle strength were 26 and 18 kg in men and women, respectively.20 The cross-sectional area of the abdominal skeletal muscles at the third lumbar vertebra was measured using a CT image analysis software (sliceOmatic V4.3; TomoVision, Magog, Canada), and skeletal muscle index (SMI) was calculated.21 The SMI cut-off values to identify low muscle mass were 42 and 38 cm²/m² in men and women, respectively.20 According to the diagnostic criteria for sarcopenia, patients with low muscle strength and low muscle mass were diagnosed with sarcopenia.20
Subjective global assessment was routinely performed by our registered dietitian on admission in a subjective manner. SGA was based on the nutritional variables (height, weight, and BMI), patient history (weight change, dietary intake, gastrointestinal symptoms, and functional capacity), and physical appearance (muscle wasting, subcutaneous fat loss, and hepatic oedema or ascites). Based on these evaluations, patients were classified into three groups: SGA-A, a well-nourished group; SGA-B, a mild or moderately malnourished group; and SGA-C, a severely malnourished group.

Royal Free Hospital-global assessment

Royal Free Hospital-global assessment uses BMI, MAMC, and dietary intake. In order to calculate BMI, objective scale weight was used if patients had no ascites or pedal oedema, whereas estimated dry weight was used if they were present. Estimated dry weight was calculated by subtracting 5% of the weight for mild ascites, 10% for moderate ascites, and 15% for severe ascites. If bilateral pedal oedema was present, MAMC was calculated using the following formula: MAMC (cm) = AC (cm) − 0.314 × TSF (cm). MAMC was subsequently compared with the Japanese reference values published by the Japanese Nutritional Assessment Study Group. Recent dietary intake was assessed using a diet history method and was classified into three groups. If intake met the estimated requirements, it was categorized as an adequate group. If intake did not meet the estimated requirements, but exceeded 500 kcal/day, it was categorized as an inadequate group. If intake was 500 kcal/day or less, it was categorized as an inadequate group. If intake did not meet the estimated requirements, it was categorized as an inadequate group. If intake met the estimated requirements, it was categorized as an adequate group. According to the RFH-GA criterion, patients are divided into three groups: adequately nourished, moderately malnourished, and severely malnourished.

Statistical analysis

Continuous variables were tested for normality using Shapiro–Wilk normality test. Baseline characteristics were presented as numbers with percentages for categorical variables and median with interquartile range for continuous variables. In univariate analyses, the Pearson’s χ² test was used for categorical variables and the Mann–Whitney U test for continuous variables. SGA-B and SGA-C patients were combined as the SGA-B/C group, and moderately and severely malnourished patients assessed by RFH-GA were combined as the malnourished group.

Baseline characteristics associated with sarcopenia were analysed using logistic regression analysis, and the results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Univariate analysis was conducted using variables including age, sex, aetiology, HCC, ascites, HE, MELD score, sodium, albumin, ammonia, SGA, and RFH-GA. Variables with P < 0.10 in univariate analysis were included in the multivariate models. Factors associated with mortality in patients with cirrhosis were analysed using the univariate and multivariate Cox proportional hazard models, and the results were presented as hazard ratios (HRs) with 95% CIs. Cumulative survival rates were evaluated using the Kaplan–Meier method, and differences between the groups were compared using the log-rank test.

All tests were two-sided, and P-values less than 0.05 were considered to indicate statistical significance. All analyses were performed using JMP Version 9.0.2 software (SAS Institute Inc., North Carolina, USA).

Results

Prevalence of sarcopenia

In the present study, the median age was 70 years, and 161 patients (67%) were men (Table 1). The most common aetiology was hepatitis C virus (64%), followed by alcohol-related liver disease (15%), other aetiologies (12%), and hepatitis B virus (9%). Of the enrolled patients, HCC, ascites, and HE were documented in 68%, 25%, and 4%, respectively.

The prevalence of sarcopenia was 11%, 23%, and 28% in SGA-A, SGA-B, and SGA-C, respectively, and was significantly higher in men (HGS, 24 kg; SMI, 43.0 cm²/m²; P < 0.001) compared with women (HGS, 19 kg; SMI, 39.9 cm²/m²; P < 0.001, respectively). Of the enrolled patients, 96 (40%) had low muscle strength, 86 (36%) showed low muscle mass, and consequently, 40 (17%) were diagnosed with sarcopenia. Patients with sarcopenia had significantly higher age and lower BMI, albumin, MAC, MAMC, SMI, and HGS than those without sarcopenia.

Table 1. The SGA-B/C group had significantly lower MAC, MAMC, and HGS, and had more advanced liver disease in terms of ascites, HE, MELD score, total bilirubin, sodium, international normalized ratio, albumin, and ammonia, compared with the SGA-A group (Table 2). No significant difference in SMI was observed between the two groups (P = 0.059).

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Subjective global assessment and sarcopenia

The distribution of each SGA group was 57% in A, 31% in B, and 12% in C in the enrolled patients (Table 1). The SGA-B/C group had significantly lower MAC, MAMC, and HGS, and had more advanced liver disease in terms of ascites, HE, MELD score, total bilirubin, sodium, international normalized ratio, albumin, and ammonia, compared with the SGA-A group (Table 2). No significant difference in SMI was observed between the two groups (P = 0.059).
Patients with sarcopenia were more frequently classified as SGA-B (43% vs. 29%) and SGA-C (20% vs. 11%) than those without sarcopenia, whereas patients without sarcopenia were more frequently classified as SGA-A (61% vs. 38%) than those with sarcopenia (Table 1).

### Table 1 Clinical characteristics of patients with and without sarcopenia

| Characteristic                      | All patients (n = 240) | No sarcopenia (n = 200) | Sarcopenia (n = 40) | P-value* |
|------------------------------------|------------------------|-------------------------|---------------------|----------|
| Age (years)                        | 70 (63–78)             | 69 (62–77)              | 78 (75–81)          | <0.001   |
| Men                                | 161 (67)               | 140 (70)                | 21 (53)             | 0.032    |
| BMI (kg/m²)                        | 22.6 (20.4–24.8)       | 22.9 (20.7–25.0)        | 20.3 (17.9–22.8)    | <0.001   |
| Aetiology                          |                        |                         |                     | 0.054    |
| HBV                                | 21 (9)                 | 20 (10)                 | 1 (3)               |          |
| HCV                                | 152 (64)               | 123 (62)                | 30 (75)             |          |
| ALD                                | 37 (15)                | 35 (18)                 | 2 (5)               |          |
| Others                             | 29 (12)                | 22 (11)                 | 7 (18)              |          |
| Hepatocellular carcinoma           | 162 (68)               | 131 (66)                | 31 (78)             | 0.139    |
| Ascites                            | 60 (25)                | 46 (23)                 | 14 (35)             | 0.109    |
| Hepatic encephalopathy             | 10 (4)                 | 9 (5)                   | 1 (3)               | 0.563    |
| SGA                                |                        |                         |                     | 0.023    |
| SGA-A                              | 136 (57)               | 121 (61)                | 15 (38)             |          |
| SGA-B                              | 75 (31)                | 58 (29)                 | 17 (43)             |          |
| SGA-C                              | 29 (12)                | 21 (11)                 | 8 (20)              |          |
| RFH-GA                             |                        |                         |                     | <0.001   |
| Adequately nourished               | 158 (66)               | 140 (70)                | 18 (45)             |          |
| Moderately malnourished            | 75 (31)                | 57 (29)                 | 18 (45)             |          |
| Severely malnourished              | 7 (3)                  | 3 (2)                   | 4 (10)              |          |
| MELD score                         | 8 (6–10)               | 8 (7–10)                | 8 (6–9)             | 0.263    |
| Total bilirubin (mg/dL)            | 1.0 (0.7–1.6)          | 1.0 (0.7–1.6)           | 0.9 (0.7–1.4)       | 0.618    |
| Creatinine (mg/dL)                 | 0.73 (0.61–0.88)       | 0.73 (0.61–0.88)        | 0.75 (0.62–0.91)    | 0.580    |
| Sodium (mEq/L)                     | 139 (137–140)          | 139 (137–140)           | 138 (136–140)       | 0.155    |
| INR                                | 1.04 (0.97–1.12)       | 1.05 (0.97–1.13)        | 1.01 (0.98–1.10)    | 0.236    |
| Albumin (g/dL)                     | 3.6 (3.1–4.0)          | 3.6 (3.2–4.0)           | 3.4 (2.9–3.8)       | 0.047    |
| Ammonia (μg/dL)                    | 53 (40–74)             | 54 (41–74)              | 49 (37–64)          | 0.165    |
| Mid-arm circumference (cm)         | 25 (24–28)             | 26 (24–29)              | 24 (22–26)          | <0.001   |
| Triceps skinfold thickness (mm)    | 9 (6–14)               | 9 (6–14)                | 9 (6–15)            | 0.538    |
| Mid-arm muscle circumference (cm)  | 22 (21–24)             | 23 (21–24)              | 21 (19–22)          | <0.001   |
| Handgrip strength (kg)             | 24 (19–32)             | 27 (21–33)              | 17 (14–20)          | <0.001   |
| Skeletal muscle index (cm²/m²)     | 43.0 (38.6–49.5)       | 44.9 (40.5–50.2)        | 37.5 (33.2–38.9)    | <0.001   |

**ALD**, alcohol-related liver disease; **BMI**, body mass index; **HBV**, hepatitis B virus; **HCV**, hepatitis C virus; **INR**, international normalized ratio; **MELD**, model for end-stage liver disease; **RFH-GA**, Royal Free Hospital-global assessment; **SGA**, subjective global assessment.

Values are presented as numbers (percentages) or medians (interquartile ranges).

*The χ² test for categorical variables or Mann–Whitney U test for continuous variables was used to compare the clinical characteristics between the two groups.

Higher in SGA-C than in SGA-A patients (P = 0.023; Table 1). Patients with sarcopenia were more frequently classified as SGA-B (43% vs. 29%) and SGA-C (20% vs. 11%) than those without sarcopenia, whereas patients without sarcopenia were more frequently classified as SGA-A (61% vs. 38%) than those with sarcopenia (Table 1).

### Royal Free Hospital-global assessment and sarcopenia

The median values of BMI and MAMC were 22.6 kg/m² and 22 cm, respectively. The percentage of recent dietary intake classified as adequate, inadequate, and negligible groups was 79%, 14%, and 7%, respectively. Among the enrolled patients, 66%, 31%, and 3% were classified as adequately nourished, moderately malnourished, and severely malnourished, respectively (Table 1).

The malnourished group (moderately and severely malnourished patients) had significantly lower adipose tissue, skeletal muscle mass, and muscle strength and had more advanced liver disease than the adequately nourished group (Table 3). Alcohol-related liver disease was significantly more frequent in malnourished patients assessed by SGA and RFH-GA (Tables 2 and 3). The prevalence of sarcopenia was 11% in the adequately nourished group, 24% in the moderately malnourished group, and 57% in the severely malnourished group (P < 0.001; Table 1).

### Factors associated with sarcopenia

Univariate logistic regression analysis revealed that age, sex, aetiology, albumin, SGA, and RFH-GA were significantly associated with sarcopenia. After adjustment for age, sex, aetiology, and albumin, multivariate analysis found that RFH-GA was a significant predictor of sarcopenia (OR, 2.47; 95% CI, 1.15–5.33; P = 0.021), but the SGA did not show statistical significance (OR, 2.10; 95% CI, 0.78–5.65; P = 0.195) (Table 4). Regarding factors associated with low muscle mass, univariate logistic regression analysis revealed that age, sex, aetiology, HE, international normalized ratio, ammonia, and RFH-GA were significantly associated with low muscle mass, but the SGA did not show statistical significance (OR, 1.14; P = 0.139) (Table 4).
### Table 2  Clinical characteristics of patients divided by the subjective global assessment categories

| Characteristic                | SGA-A (n = 136) | SGA-B (n = 75) | SGA-C (n = 29) | P-value
|------------------------------|-----------------|----------------|----------------|--------
| Age (years)                  | 70 (63–78)      | 76 (65–79)     | 69 (65–75)     | 0.131  |
| Men                          | 91 (67)         | 49 (65)        | 21 (72)        | 0.948  |
| BMI (kg/m²)                  | 22.8 (20.6–25.0) | 22.4 (20.2–24.4) | 22.4 (19.7–25.0) | 0.149  |
| Aetiology                    |                 |                |                | 0.035  |
| HBV                          | 14 (10)         | 5 (7)          | 2 (7)          |        |
| HCV                          | 92 (68)         | 49 (65)        | 12 (41)        |        |
| ALD                          | 13 (15)         | 12 (16)        | 12 (41)        |        |
| Others                       | 17 (13)         | 9 (12)         | 3 (10)         |        |
| Hepatocellular carcinoma     | 92 (68)         | 55 (73)        | 15 (52)        | 0.956  |
| Ascites                      | 7 (5)           | 27 (36)        | 26 (90)        | <0.001 |
| Hepatic encephalopathy       | 0               | 7 (9)          | 3 (10)         | <0.001 |
| MELD score                   | 7 (6–8)         | 9 (7–10)       | 12 (10–17)     | <0.001 |
| Total bilirubin (mg/dL)      | 0.8 (0.7–1.1)   | 1.3 (0.9–1.7)  | 2.3 (1.0–3.8)  | <0.001 |
| Creatinine (mg/dL)           | 0.75 (0.60–0.86)| 0.73 (0.61–0.95)| 0.71 (0.62–0.92)| 0.726  |
| Sodium (mEq/L)               | 139 (137–140)   | 138 (137–140)  | 136 (134–140)  | 0.004  |
| INR                          | 1.01 (0.96–1.06)| 1.09 (1.01–1.16)| 1.15 (1.08–1.35)| <0.001 |
| Albumin (g/dL)               | 3.9 (3.6–4.1)   | 3.3 (3.0–3.5)  | 2.6 (2.3–2.8)  | <0.001 |
| Ammonia (µg/dL)              | 49 (38–63)      | 40 (62–85)     | 74 (47–100)    | <0.001 |
| Mid-arm circumference (cm)   | 27 (24–28)      | 25 (24–27)     | 23 (20–25)     | <0.001 |
| Triceps skinfold thickness (mm)| 9 (6–15)     | 9.6 (14–16)    | 6 (3–13)       | 0.056  |
| Mid-arm muscle circumference (cm)| 23 (21–24) | 22 (20–23)     | 21 (18–22)     | <0.001 |
| Handgrip strength (kg)       | 28 (20–34)      | 23 (17–30)     | 20 (18–23)     | <0.001 |
| Skeletal muscle index (cm²/m²)| 43.8 (38.6–51.5)| 41.9 (38.8–47.8)| 42.4 (37.4–47.0)| 0.059  |

ALD, alcohol-related liver disease; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease; SGA, subjective global assessment.

Values are presented as numbers (percentages) or medians (interquartile ranges).

*The χ² test for categorical variables or Mann–Whitney U test for continuous variables was used to compare the clinical characteristics between the SGA-A and SGA-B/C groups.

### Table 3  Clinical characteristics of patients divided by the Royal Free Hospital-global assessment categories

| Characteristic | Adequately nourished (n = 158) | Moderately malnourished (n = 75) | Severely malnourished (n = 29) | P-value
|----------------|---------------------------------|-----------------------------------|---------------------------------|--------
| Age (years)    | 70 (63–78)                      | 74 (66–80)                        | 70 (51–79)                      | 0.180  |
| Men            | 107 (68)                        | 48 (64)                           | 6 (86)                          | 0.770  |
| BMI (kg/m²)    | 23.6 (21.8–25.1)                | 19.9 (18.7–22.8)                  | 17.5 (16.7–19.8)                | <0.001 |
| Aetiology      |                                 |                                   |                                 | 0.008  |
| HBV            | 17 (11)                         | 3 (4)                             | 1 (14)                          |        |
| HCV            | 103 (65)                        | 47 (63)                           | 3 (43)                          |        |
| ALD            | 16 (10)                         | 18 (24)                           | 3 (43)                          |        |
| Others         | 22 (14)                         | 7 (9)                             | 0                               |        |
| Hepatocellular carcinoma | 108 (68) | 50 (67) | 4 (57) | 0.695 |
| Ascites        | 29 (18)                         | 25 (33)                           | 6 (86)                          | 0.001  |
| Hepatic encephalopathy | 7 (4) | 3 (4) | 0 | 0.777 |
| MELD score     | 7 (6–9)                         | 8 (7–11)                          | 16 (8–18)                       | 0.008  |
| Total bilirubin (mg/dL) | 0.9 (0.7–1.5) | 1.0 (0.8–1.6) | 1.0 (0.8–7.6) | 0.163 |
| Creatinine (mg/dL) | 0.74 (0.61–0.87) | 0.71 (0.60–0.89) | 0.78 (0.69–1.17) | 0.805 |
| Sodium (mEq/L) | 139 (137–140)                   | 138 (136–140)                     | 137 (133–142)                   | 0.002  |
| INR            | 1.03 (0.97–1.11)                | 1.05 (1.00–1.13)                  | 1.16 (1.11–1.29)                | 0.019  |
| Albumin (g/dL) | 3.7 (3.3–4.1)                   | 3.5 (3.1–3.8)                     | 2.6 (2.2–2.8)                   | <0.001 |
| Ammonia (µg/dL) | 53 (41–78) | 39 (49–67) | 53 (72–85) | 0.342 |
| Mid-arm circumference (cm) | 27 (25–29) | 24 (22–25) | 19 (16–22) | <0.001 |
| Triceps skinfold thickness (mm) | 10 (7–15) | 7 (5–11) | 5 (2–6) | <0.001 |
| Mid-arm muscle circumference (cm) | 23 (22–25) | 21 (20–22) | 18 (15–20) | <0.001 |
| Handgrip strength (kg) | 26 (20–33) | 22 (18–30) | 20 (17–23) | 0.007 |
| Skeletal muscle index (cm²/m²) | 44.8 (40.2–51.6) | 40.6 (36.0–45.8) | 33.7 (24.1–39.3) | <0.001 |

ALD, alcohol-related liver disease; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease.

Values are presented as numbers (percentages) or medians (interquartile ranges).

*The χ² test for categorical variables or Mann–Whitney U test for continuous variables was used to compare the clinical characteristics between the nourished and malnourished groups.

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95% CI, 0.67–1.93; P = 0.638). After adjustment for these variables, multivariate analysis found that RFH-GA (OR, 3.28; 95% CI, 1.72–6.28; P < 0.001) was a significant predictor of low muscle mass (Supporting Information, Table S1). Regarding factors associated with low muscle strength, univariate logistic regression analysis revealed that age, aetiology, HCC, ascites, MELD score, albumin, SGA (OR, 3.51; 95% CI, 2.04–6.03; P < 0.001), and RFA-GA (OR, 2.18; 95% CI, 1.27–3.77; P = 0.005) were significantly associated with low muscle strength. After adjustment for these variables, multivariate analysis found that there was no relationship between low muscle strength and SGA or RFH-GA (Table S2).

### Nutritional assessment and survival

During a median follow-up of 2.7 years (interquartile range, 0.9–5.2), 113 (47%) patients died. The causes of death were HCC (72%), liver failure (15%), infections (3%), and other reasons (11%). No patient underwent liver transplantation during the follow-up period. The overall survival rates were significantly lower in the SGA-B/C group than in the SGA-A group (P < 0.001; Figure 1A). Similarly, in RFH-GA, the survival rates were significantly lower in the malnourished group than in the nourished group (P < 0.001; Figure 1B).

### Factors associated with mortality

The univariate Cox hazard regression analysis found that age, HCC, ascites, MELD score, sodium, albumin, ammonia, SGA, and RFH-GA were significant risk factors for mortality. After adjustment for these variables, multivariate analysis found that SGA (HR, 1.99; 95% CI, 1.19–3.32; P = 0.009) and RFH-GA (HR, 1.51; 95% CI, 1.02–2.23; P = 0.041) independently predicted mortality in patients with CLD (Table 5).

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**Table 4** Factors associated with sarcopenia in patients with chronic liver disease

| Characteristic                           | Univariatea | Multivariatea,b |
|-----------------------------------------|-------------|-----------------|
|                                         | OR (95% CI) | P-value         | OR (95% CI) | P-value         |
| SGA (B/C vs. A)                         | 2.55 (1.27–5.14) | 0.009         | 2.10 (0.78–5.65) | 0.139         |
| RFH-GA (malnourished vs. nourished)     | 2.85 (1.43–5.70) | 0.003         | 2.47 (1.15–5.33) | 0.021         |

CI, confidence interval; OR, odds ratio; RFH-GA, Royal Free Hospital-global assessment; SGA, subjective global assessment.

a Logistic regression analysis.

b Adjusting for age, sex, aetiology, and albumin (variables with a P-value < 0.1 in univariate analysis).

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In the subgroup analysis of RFH-GA, we compared the survival rates between the nourished and malnourished groups for each sex. The overall survival rates in men were significantly lower in the malnourished group than in the nourished group (P = 0.002; Figure 2A), but this difference was not observed in women (P = 0.063; Figure 2B). Additionally, lower MAMC was significantly associated with higher mortality in men (HR, 1.12; 95% CI, 1.02–1.22; P = 0.013), but not in women (HR, 1.15; 95% CI, 0.99–1.39; P = 0.084), whereas lower TSF was associated with higher mortality in women (HR, 1.07; 95% CI, 1.01–1.14; P = 0.014), but not in men (HR, 1.03; 95% CI, 0.97–1.09; P = 0.367).

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Figure 1 (A) Overall survival of 136 SGA-A and 104 SGA-B/C patients. (B) Overall survival of 158 nourished and 82 malnourished patients assessed by Royal Free Hospital-global assessment. Overall survival was estimated using the Kaplan–Meier method and compared between groups using the log-rank test. SGA, subjective global assessment.

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Discussion

This retrospective study has several clinically important findings. First, our findings reveal that patients with sarcopenia have a higher risk of malnutrition than those without sarcopenia. Second, RFH-GA, but not SGA, can be a predictive factor for sarcopenia in patients with CLD. Third, RFH-GA as well as SGA is associated with an increased risk of mortality, independent of the degree of liver dysfunction and HCC. These findings provide new evidence that RFH-GA not only assesses malnutrition but also predicts sarcopenia and mortality in patients with CLD.

Diagnosing sarcopenia can identify patients who would potentially benefit from therapeutic intervention, including nutritional supplementation and/or exercise therapy, both of which contribute to improved clinical outcomes for patients with sarcopenia. Physicians are therefore recommended to repeatedly perform the assessment of sarcopenia in patients with CLD. However, the diagnosis of sarcopenia is limited in daily clinical practice because the routine use of CT images generally involves the cost, radiation exposure, and/or time-consuming procedures. Repeatable nutritional assessment methods that are clinically easily available at the bedside are thus required for identifying patients at risk of sarcopenia and predicting their outcomes.

Severely malnourished patients in RFH-GA, which is determined by BMI and MAMC, had a lower SMI than adequately nourished patients, but these relationships were not noted in SGA. These findings agree with those of a previous study demonstrating an association between RFH-GA and skeletal muscle mass in liver transplant patients. Recent evidence shows that BMI and anthropometric measurements are reliable predictors of sarcopenia in patients with CLD, especially in cirrhotic patients. BMI can predict sarcopenia, independent of age, sex, and liver function reserves in liver transplant patients. It is also reported that assessment of BMI and thigh muscle thickness, which significantly correlates with CT imaging-based sarcopenia, is a simple and inexpensive model to identify sarcopenia in patients with cirrhosis.

For these reasons, we consider that the prediction of sarcopenia requires BMI and muscle mass measurements, both of which are factors constituting RFH-GA, and thus, RFH-GA potentially has an advantage over SGA in predicting sarcopenia.

Subjective global assessment has good inter-observer reproducibility and is used worldwide to screen for malnutrition in various diseases. However, the validity of SGA for evaluating nutritional status in liver disease has been controversial. Several studies have shown that SGA underestimates the prevalence of malnutrition and presents...
low agreement with other nutritional assessment methods. Our findings on the relationship between SGA and sarcopenia revealed that SGA has no ability to predict sarcopenia. This result agrees with those of previous studies in that SGA has no association with muscle mass. Some studies on liver transplantation have shown a low concordance between SGA and sarcopenia, whereas other studies have confirmed no statistical association between SGA and sarcopenia. Therefore, we presume that SGA, as compared with RFH-GA, has a limited capacity to predict sarcopenia in patients with liver disease.

Another important finding in our study is that RFH-GA can predict mortality, regardless of HCC and liver disease severity. However, the relationship between RFH-GA and mortality is significant only in men, but not in women. These findings are in good agreement with those of other studies in that RFH-GA can predict mortality in men, but not in women. This sex disparity in survival can be explained in part by the fact that there are intrinsic gender differences in fat distribution, muscle and fat metabolism, and hormonal characteristics. Because women have greater adipose tissue than men, women at risk of malnutrition are more likely to use fat tissue as a source of energy than muscle mass. This mechanism may result in relatively preserved muscle mass in women longer before developing sarcopenia. Lower subcutaneous fat in women is associated with a higher risk of mortality, whereas decreased muscle mass in men is associated with mortality. Similarly, the results of our study show that lower MAMC in men and lower TSF in women are associated with mortality, and thus, gender differences in muscle and fat may partially explain this discrepancy in survival. Therefore, in order to screen patients with CLD at high risk of mortality, appropriate assessment of body composition and its changes should be repeatedly performed based on gender differences.

The present study has several limitations. First, the sample size was relatively small. A total of 240 patients may be insufficient to determine the association between sarcopenia and nutritional assessment methods in detail. However, from the results of the limited number of patients, our findings show that RFH-GA can be a predictive factor for sarcopenia. Second, because this study was performed at a single institution, our results might not be generalizable to other cohorts and regions. Third, our research is limited by the fact that a 24 h dietary recall method was used to assess recent dietary intake of patients. Difficulties exist in accepting the reliability of this approach because it depends mostly on the patient’s recall ability and might not accurately exhibit routine food choices and behaviours. Finally, although we used multivariate analysis to adjust for bias, the retrospective nature of this study limits the assessment of other variables that enable interpretation of results and potential assignment of causation.

In conclusion, our findings provide additional evidence that patients with malnutrition are at a high risk for sarcopenia. RFH-GA is a simple, inexpensive, non-invasive, and useful bedside screening method for assessing malnutrition, identifying sarcopenia, and predicting mortality in patients with CLD. These findings improve our knowledge of the link between nutritional assessment methods and sarcopenia.

Author contributions

All authors contributed to the study conception and design; Tatsunori Hanai, Makoto Shiraki, Kayoko Nishimura, Yui Ogiso, Kenji Imai, Atsushi Suetsugu, and Koji Takai collected the data; Tatsunori Hanai and Makoto Shiraki performed the statistical analysis; Tatsunori Hanai and Makoto Shiraki wrote the first draft of the manuscript; and all authors commented on previous versions of the manuscript. All authors have read and approved the final version of the manuscript.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Factors associated with low muscle mass in patients with chronic liver disease.

Table S2. Factors associated with low muscle strength in patients with chronic liver disease.

Conflict of interest

The authors declare that they have no conflict of interest.

Authorship statement

The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle.
Ethical statement

Informed consent from the participants was obtained using an opt-out approach because of the retrospective nature of this study, and personal information was protected during data collection. The study protocol was reviewed and approved by the ethics committee of the Gifu University Graduate School of Medicine, and the study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

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