Research article

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Rectus femoris ultrasound identifies sarcopenia and predicts poor outcomes in patients with acute decompensation of cirrhosis

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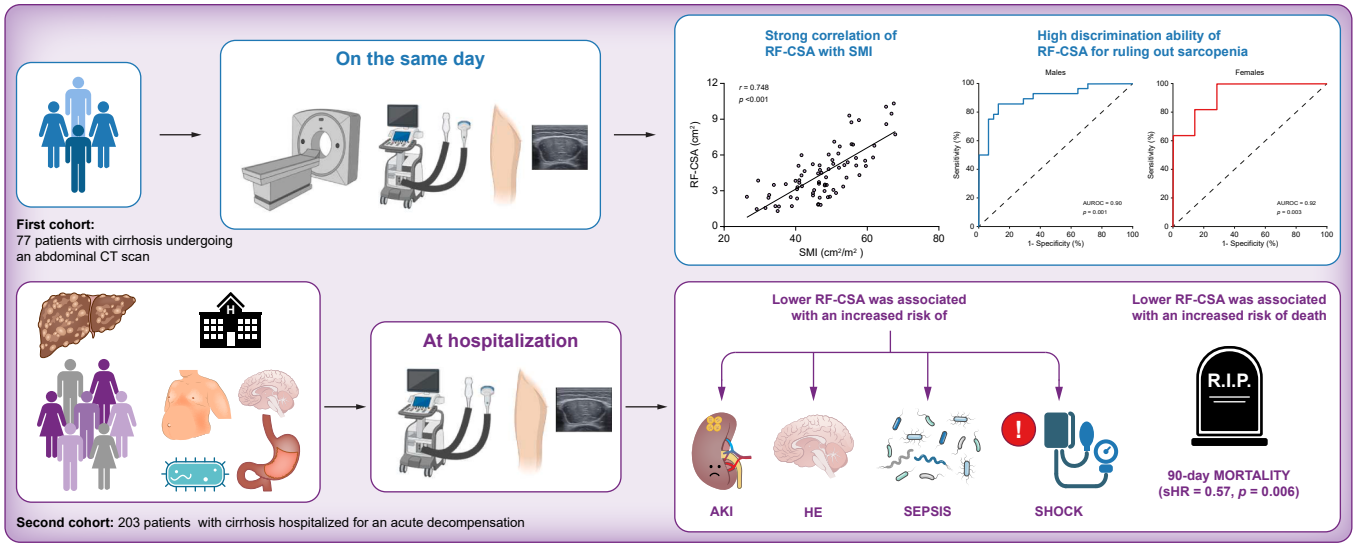
Graphical abstract



Highlights:

- Sarcopenia is frequent in cirrhosis and linked to poor clinical outcomes.
- RF-CSA measured by ultrasound is accurate for assessing muscle mass.
- Thigh ultrasound can be used as a point-of-care tool for assessing sarcopenia.
- RF-CSA is associated with complications and mortality.

Impact and implications:

Sarcopenia is strongly associated with adverse clinical outcomes in patients with cirrhosis. However, its assessment remains infrequent in clinical practice because of the reliance on CT-based SMI measurements, which are costly, expose patients to radiation, and require specialized software. This study demonstrates that bedside ultrasound measurement of RF-CSA is a simple, accurate, and reliable alternative for assessing sarcopenia in patients with decompensated cirrhosis. RF-CSA not only correlates well with SMI, but also independently predicts sarcopenia, complications, and 90-day mortality. Its strong prognostic value underscores its potential for routine use in clinical practice. Moreover, RF-CSA assessment is easy to learn, highly reproducible across different operators, and feasible for point-of-care application. These findings support the integration of ultrasound-based muscle assessment into routine cirrhosis management, enabling early risk stratification and potentially guiding targeted interventions to improve patient outcomes.

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Rectus femoris ultrasound identifies sarcopenia and predicts poor outcomes in patients with acute decompensation of cirrhosis☆

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Background & Aims: Sarcopenia is common and associated with poor outcomes in decompensated cirrhosis. While computed tomography (CT) scan, with measurement of skeletal muscle index (SMI) at L3, is the gold standard for assessing sarcopenia in patients with cirrhosis, it is costly, exposes patients to radiation, and requires specialized software. This study evaluated the accuracy of bedside ultrasound measurement of the rectus femoris cross-sectional area (RF-CSA) in assessing sarcopenia and its prognostic value in patients with cirrhosis.

Methods: A prospective two-phase study was conducted. Phase 1 analyzed correlations between RF-CSA and SMI, as well as other sarcopenia predictors, in 77 patients. In phase 2, RF-CSA was measured at the bedside in 203 patients with acute decompensation of cirrhosis, followed up until death, liver transplant, or 90 days. Interoperator reliability was assessed in 38 patients using the intraclass correlation coefficient (ICC).

Results: RF-CSA strongly correlated with SMI (r = 0.748, p <0.001), outperforming muscle thickness and anthropometric parameters. RF-CSA was an independent predictor of sarcopenia (hazard ratio (HR) = 0.27, p <0.001) and demonstrated high discrimination ability for sarcopenia (AUROC = 0.90 in men and 0.92 in women). Lower RF-CSA was independently associated with an increased risk of developing sepsis, acute kidney injury, shock, and overt hepatic encephalopathy. RF-CSA was an independent predictor of 90-day mortality (subdistribution HR = 0.57, p = 0.006). Intra- and interoperator reliability were high (ICC = 0.980 and 0.947, respectively, p <0.001 for both).

Conclusions: RF-CSA assessment by thigh ultrasound is an accurate, reliable, and easy point-of-care tool for assessing sarcopenia in patients with decompensated cirrhosis. It is also associated with the risk of complications and mortality.

Introduction

Patients with cirrhosis frequently have a reduction in muscle mass and muscle strength because of malnutrition, reduced mobility, systemic hypermetabolism and accelerated 'starvation', endotoxin release for bacterial translocation, systemic inflammation, hyperammonemia, insulin resistance, and hormonal changes.[1] Sarcopenia in patients with cirrhosis is associated with a higher risk of complications,[2–4] such as bacterial infections, hepatic encephalopathy (HE), ascites, and a longer hospital stay, as well as being an independent predictor of morbidity and mortality.[3,4] Various techniques, such as bioelectrical impedance analysis (BIA), anthropometric measures, dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), computed tomography (CT) scans, and ultrasound, have been used to assess muscle mass in patients with cirrhosis.[1] BIA and DXA are limited, mainly in decompensated patients, because they are both affected by fluid retention and ascites,[1] even though this is less relevant for the phase angle from BIA.[5] Anthropometric measurements, such as mid-arm muscle circumference (MAMC), can serve to estimate skeletal muscle mass, at the cost of reduced test sensitivity and reproducibility.[6] Quantitative measures based on the diameter and/or the total skeletal muscle area (SMA) at the level of L3 (the psoas, paraspinals, transverse abdominals, rectus abdominis, and internal and external obliques) assessed by CT have been considered the gold standard for assessing sarcopenia in cirrhosis.[7–9] SMA is usually corrected by the squared height to calculate the skeletal muscle index (SMI). Optimal SMI cutoffs for defining sarcopenia were identified as 50 cm^2/m^2 for men and 39 cm^2/m^2 for women.[8] However, CT has many limitations related to high cost, radiation exposure,

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and the need for a specific software for SMI measurement. However, thigh ultrasonography is recognized as an accurate and reliable technique for assessing muscle size.[10] Ultrasonography has many advantages because it is not based on ionizing radiation, is widely available, and allows multiple assessments over time. Some studies have demonstrated the reliability and validity of thigh ultrasonography in the general population,[10] critical care,[11,12] and other diseases.[13] Thigh ultrasound can measure both muscle thickness and cross-sectional area (CSA). It has been shown that CSA is more reliable compared with muscle thickness in critically ill patients. A study of 159 outpatients with cirrhosis (60% Child-Pugh A) showed that right quadriceps muscle thickness was associated with sarcopenia.[14] Other small sample studies, not powered for assessing clinical outcomes, evaluated the right quadriceps muscle thickness or iliopsoas muscle thickness and area for assessing sarcopenia, with controversial results.[15] Therefore, we planned a prospective study to evaluate: (1) the accuracy of ultrasound measurement of rectus femoris cross sectional area (RF-CSA) in the assessment of sarcopenia; (2) the prognostic value of RF-CSA in patients hospitalized with cirrhosis; and (3) the intra- and interobserver reliability of RF-CSA.

Patients and methods

Study design and endpoints

The study comprised two phases. In the first phase, the primary endpoint was to evaluate the accuracy of RF-CSA in the assessment of muscle mass and sarcopenia. In the second phase, the primary endpoint was to evaluate the prognostic value of RF-CSA in patients with cirrhosis hospitalized for an acute decompensation (AD). Endpoints were: occurrence of infections/sepsis; shock; acute kidney injury (AKI); overt HE; organ failure; acute-on-chronic liver failure (ACLF); need for renal replacement therapy (RRT); need for mechanical ventilation (MV); transfer to intensive care unit (ICU); in-hospital mortality; and 90-day mortality.

Phase 1

From April 2019 to September 2020, adult patients with cirrhosis and indication for an abdominal CT scan for the characterization of liver nodules or assessment for liver transplant (LT) were screened and enrolled unless they had the following exclusion criteria: (1) diagnosis of hepatocellular carcinoma (HCC) outside the Milan criteria (a single nodule <5 cm or multiple nodules [maximum three], the largest of which ≤3 cm); (2) extrahepatic malignancies at the time of inclusion; (3) severe extrahepatic diseases (*e.g.* chronic kidney disease requiring hemodialysis, heart failure [NYHA class ≥3]; GOLD chronic obstructive pulmonary disease grade ≥3; psychiatric disorders); and (4) refusal, or inability of the patient to provide informed consent.

Demographic and clinical data were collected at inclusion; nutrition was assessed with the Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT); physical frailty was assessed with the Liver Frailty Index (LFI); and MAMC was measured. For each patient, the SMA (*i.e.* psoas, paraspinals, transverse abdominals, rectus abdominis, and internal and external obliques) at the L3 level was segmented and collected by two expert radiologists (SB and CG) using the NIH Image J software (National Institutes of Health, Bethesda, MD, USA).[16] The Hounsfield unit range was -29 to 150. SMI was obtained by dividing the SMA by the square of height in meters, using Equation 1:

$$SMI = SMA/h^2 \quad [1]$$

Sarcopenia was defined as SMI <50 cm^2/m^2 in men and <39 cm^2/m^2 in women. A thigh ultrasound was performed on the same day as the CT scan. In both cases, the procedures were conducted after a minimum of 8 h of fasting. The measurement of the RF-CSA of the right thigh was performed using a standardized protocol based on already published studies.[12,17,18] This method has shown excellent validity and reproducibility.[10] RF-CSA was measured by B-mode ultrasound using a portable ultrasound machine (MyLab XPro30, Esaote S.p.A) using a 5–15 MHz linear transducer or a 2–5 MHz convex transducer in cases where the muscle area was too large to be fully visible on the screen. The evaluation was performed with the patient in a supine position. All ultrasound measurements were performed with the probe positioned perpendicular to the long axis of the right thigh, at two-thirds of the distance from the anterior superior iliac spine to the superior patellar border, applying minimal pressure. A generous amount of gel was applied to minimize tissue compression. RF-CSA was calculated by a planimetric technique after the inner echogenic line of the rectus femoris was outlined by a movable cursor on a frozen image (Fig. 1). Three measurements were collected, and the mean was calculated. On the same freeze-framed ultrasound image, we also measured the thickness of the rectus femoris muscle. All measurements were made by two investigators from our Unit (PC and BS) who were trained by an expert radiologist (SB). Each operator was deemed autonomous after conducting at least 10 supervised examinations considered accurate. Operators were blind regarding the SMI values. In addition to the non-indexed parameters, RF-CSA was also normalized by the square of the patient's height. Details of the assessment of LFI and MAMC are provided in supplementary data.

Phase 2

Consecutive patients with cirrhosis admitted at the Unit of Internal Medicine and Hepatology of the University Hospital of Padua between October 2020 and June 2024 were screened according to the following inclusion and exclusion criteria. Inclusion criteria were: (1) age >18 years; (2) cirrhosis diagnosed by histological findings on biopsy, or based on evidence from clinical, laboratory, or instrumental data (endoscopic, ultrasound, and liver stiffness measured by transient elastography); (3) hospital admission for AD (ascites, HE, variceal bleeding, or bacterial infections); and (4) ability and will to provide written informed consent. Exclusion criteria were: (1) pregnancy; (2) diagnosis of HCC outside the Milan criteria (a single nodule <5 cm or multiple nodules (maximum 3), the largest of which ≤3 cm); (3) extrahepatic malignancies; (4) severe extrahepatic diseases (*e.g.* chronic renal failure requiring hemodialysis; heart failure (NYHA class ≥3); GOLD chronic obstructive pulmonary disease grade ≥3; or psychiatric disorders); (5) HIV infection; and (6) refusal or inability of the patient to provide informed consent. RF-CSA was measured at the bedside by three different operators

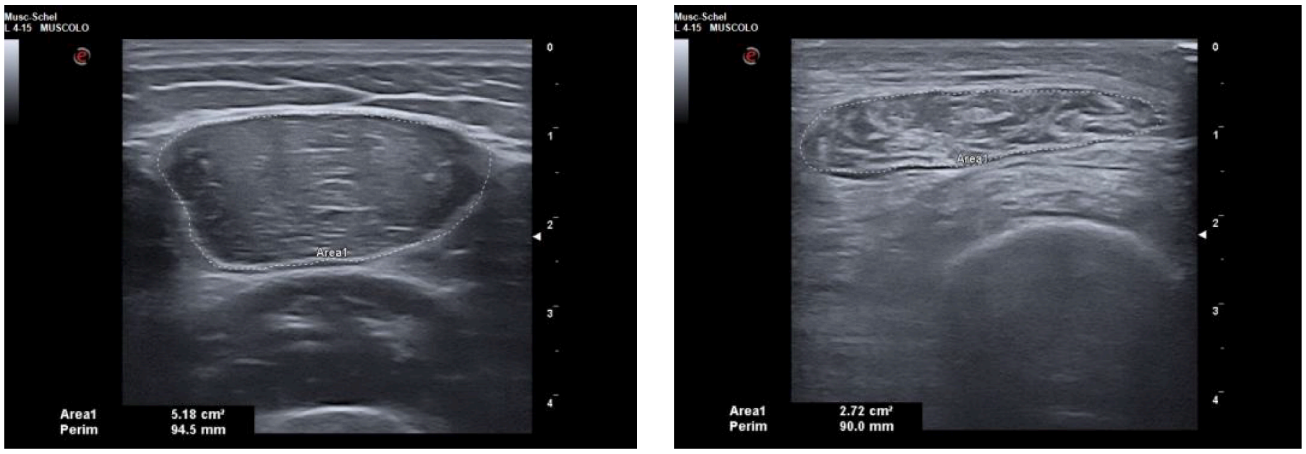

Fig. 1. Ultrasound measurement of RF-CSA by a planimetric technique in two male patients with cirrhosis, one without (left) and one with sarcopenia (right). The dashed line identifies the perimeter of the rectus femoris. RF-CSA, rectus femoris cross-sectional area.

(PC, BS, and RG), who were trained by an expert radiologist (SB). Development of complications (overt HE, infections/sepsis, shock, AKI, organ failure, and ACLF), need for RRT, MV, or ICU transfer during hospitalization was recorded. Patients were followed up until death, LT, or 90 days. In addition, we evaluated intra-operator reliability considering all three measurements of RF-CSA made by the operator on each patient. Interoperator reliability was evaluated on measurements of RF-CSA conducted by two different operators in the same day on 38 patients. Time to obtain RF-CSA was collected for each of the three measurements for each operator and then averaged across operators.

Definitions

Sarcopenia was defined based on SMI values (<39 cm^2/m^2 in women and <50 cm^2/m^2 in men), according to the literature.[8] For the diagnosis of sepsis, the Sepsis-3[19] criteria were used, whereas a diagnosis of ACLF was formulated according the EASL-CLIF consortium criteria.[20] AKI was defined according to KDIGO criteria.

Study approval and informed consent

The protocol was approved by the local Ethics Committees (218n/AO). Data were collected prospectively, and all patients gave informed consent. The study was conducted according to the principles of the declarations of Helsinki and Istanbul.

Sample size and statistical analysis

The sample size calculation for phase 1 was conducted to detect a statistically significant correlation between RF-CSA measured by thigh ultrasound and SMI measured by CT scan, which is considered the gold standard. Based on existing literature and preliminary data, we assumed a moderate correlation (Pearson correlation coefficient of 0.45) between ultrasound and CT measurements. Using a two-tailed test with a significance level (alpha) of 0.025 and a power of 90%, the minimum required sample size was estimated to be ~60 patients. For phase 2, the sample size calculation was based on the number of events needed to demonstrate the association between RF-CSA and mortality, after adjusting for age, sex, model for end-stage liver disease (MELD) score, and presence of infections. Applying the rule of thumb of 10 events per variable and assuming a 90-day mortality rate of 25%, we required a total of 200 patients.

Normally distributed continuous variables were reported as means ± SD and compared with Student's *t* test. Non-normally distributed continuous variables were reported as median ± IQR and compared with Mann-Whitney *U* test. Categorical variables were reported as count and percentage and compared with Chi-square test or Fisher's exact test, when appropriate. Correlation between SMI and anthropometric and nutritional parameters was assessed using the Pearson's correlation coefficient. The strength of the correlation among SMI and the covariates was assessed with the Steiger's test. The discrimination ability of RF-CSA for identifying sarcopenia in men and women was evaluated using the AUROC. Youden's index was used to identify the optimal RF-CSA threshold for sarcopenia. Univariable and multivariable analyses of 90-day mortality were performed using the Fine-Gray subdistribution hazard model. LT was considered a competing risk for mortality. Multivariable analyses were adjusted for age, sex, MELD score, and presence of infections. We also explored an alternative model using ACLF instead of MELD score. The subdistribution hazard ratios (sHR) and their 95% CIs were calculated. The association of RF-CSA with in-hospital and 90-day mortality was also evaluated according to tertiles of RF-CSA for men and for women. Cumulative incidence functions of mortality at 90 days were developed through competing risks analysis and compared with Gray's test. A logistic model was used to examine the predictors of in-hospital mortality, excluding transplant patients. The odds ratio (OR) and 95% CIs were calculated. To assess the effect of average RF-CSA values on events developed during hospitalization (infections,

sepsis, AKI, HE, shock, ACLF, transfer to ICU, need for RRT and MV), a logistic regression model adjusted for age, sex, and MELD was applied for each type of event. The OR and 95% CIs were calculated. Analyses were performed with R 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Phase 1

Study population

We enrolled 77 patients in phase 1 of the study. The characteristics of this study population at enrolment are shown in Table 1. The mean age was 62 ± 9 years and 77% of patients were men. The most common etiology of cirrhosis was alcohol (55%), followed by metabolic dysfunction-associated steatotic liver disease (MASLD) (29%) and HCV (26%). The mean MELD score was 16 ± 6 points. Twenty-eight out of 77 patients (36%) had HCC. At enrolment, 70% of patients had ascites and 20% showed HE. The median BMI was 27 kg/m^2 (IQR 24–32). Measurement of SMI reported a median value of 48.1 cm^2/m^2 (IQR 41.6–54.4) across the whole population, 49.2 cm^2/m^2 in men (IQR 43.7–55.6), and 43.3 cm^2/m^2 in women (IQR 35.1–46.9), and 38 patients (49%) had sarcopenia. The median value of RF-CSA was 4.1 cm^2 (IQR 2.8–5.6) across the whole population, 4.7 cm^2 in men (IQR 3.5–6.0) and 2.6 cm^2 (IQR 1.7–3.5) in women. Measurement of RF-CSA was performed with a linear transducer in 65 patients and with a convex transducer in 12 patients.

Correlation of RF-CSA with SMI and patients' characteristics according to RF-CSA values

RF-CSA showed a strong correlation with both SMI (r = 0.748; p <0.001; Fig. 2A) and SMA (r = 0.768; p <0.001; Fig. 2B) outperforming RF thickness, BMI, MAMC, LFI, and RFH-NPT (Tables S1 and S2; Steiger's test <0.01 for all comparisons). The correlation between RF-CSA indexed by height squared and SMI was similarly strong to that of the unindexed RF-CSA (r = 0.737; p <0.001). The correlation between RF-CSA and SMI remained robust across different BMI strata. We observed a good correlation in non-overweight (BMI <25 kg/m^2) *vs.* overweight (BMI ≥25 kg/m^2) patients (r = 0.71 *vs.* 0.73; p <0.001 for both), as well as in non-obese (BMI <30 kg/m^2) *vs.* obese (BMI ≥30 kg/m^2) patients (r = 0.72 *vs.* 0.74; p <0.001 for both). Characteristics of patients with or without sarcopenia are reported in Table 1. Patients with sarcopenia had worse

Table 1. Characteristics of patients included in phase 1 with or without sarcopenia.

Variable	All patients (n = 77)	No sarcopenia (n = 39)	Sarcopenia (n = 38)	*p* value
Age, years; mean (SD)	62 (9)	63 (9)	61 (10)	0.286
Sex, male; n (%)	59 (77)	28 (72)	31 (82)	0.310
Ethnicity; n (%)				
White	76 (98.7)	39 (100)	37 (97.4)	0.4935
Asian	1 (1.3)	0 (0)	1 (2.6)	
Etiology; n (%)				
Alcohol	42 (55)	21 (54)	21 (55)	1.000
HCV	20 (26)	14 (36)	6 (16)	0.080
HBV	8 (10)	2 (5)	6 (16)	0.246
MASLD	22 (29)	11 (28)	11 (29)	1.000
Other	14 (18)	6 (15)	8 (21)	0.727
Compensated; n (%)	12 (15.6)	11 (28)	1 (2.6)	0.003
MELD score; mean (SD)	16 (6)	15 (6)	18 (6)	0.022
Child-Pugh score; median (IQR)	9 (7–11)	9 (5–10)	10 (8–11)	0.058
MAP, mmHg; median (IQR)	82 (75–90)	83 (73–93)	81 (76–87)	0.291
WBC, x10^9/L; median (IQR)	5.1 (3.4–7.3)	4.9 (2.9–6.7)	5.3 (4.0–8.7)	0.129
Hemoglobin, g/dl; median (IQR)	10.5 (9.1–12.2)	10.5 (9.1–12.2)	10.0 (9.1–11.6)	0.050
Platelets, x10^9/L; median (IQR)	85 (54–115)	85 (54–115)	84 (50–133)	0.992
INR; median (IQR)	1.4 (1.3–1.8)	1.4 (1.3–1.8)	1.4 (1.3–1.7)	0.618
Bilirubin, µmol/L; median (IQR)	37 (19–115)	37 (19–115)	46 (24-192)	0.124
Creatinine, µmol/L; median (IQR)	77 (62–98)	77 (62–98)	72 (55-102)	0.318
Sodium, mmol/L; mean (SD)	137 (5)	138 (4)	135 (5)	0.007
Albumin, g/L; median (IQR)	30 (27–34)	31 (28–37)	29 (24 - 32)	0.049
CRP, mg/L; median (IQR)	19 (8–57)	19 (8–57)	35 (14-62)	0.058
HCC; n (%)	28 (36)	15 (39)	13 (34)	0.880
Diabetes; n (%)	32 (42)	16 (41)	16 (42)	1.000
Ascites; n (%)	54 (70)	21 (54)	33 (87)	0.004
HE; n (%)	15 (20)	7 (18)	8 (21)	0.955
BMI, kg/m^2; median (IQR)	27 (24 - 32)	29 (26–33)	25 (22–29)	<0.001
MAMC, cm; median (IQR)	24.4 (22.0–27.4)	24.4 (22.0–27.4)	22.6 (20.2–24.9)	<0.001
LFI; median (IQR)	5.6 (4.5–6.4)	5.1 (4.2–6.2)	6.1 (4.6–6.6)	0.031
RFH-NPT; median (IQR)	2 (1–5)	2 (1–5)	3 (2–5)	0.022
RF-CSA, cm^2; median (IQR)	4.1 (2.8–5.6)	5.4 (3.7–6.9)	3.5 (2.5–4.3)	<0.001
Thickness, cm; median (IQR)	2.16 (1.5–2.61)	2.43 (2.16–2.85)	1.80 (1.44–2.15)	<0.001

Comparisons were made with Student's *t* test, Mann-Whitney *U* test, and Chi-square test or Fisher's exact test, when appropriate. CRP, C reactive protein; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalized ratio; LFI, Liver Frailty Index; MAMC, mid-arm muscle circumference; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; RF-CSA, rectus femoris cross-sectional area; RFH-NPT, Royal Free Hospital-Nutritional Prioritizing Tool; SMI, skeletal muscle index; WBCs, white blood cells.

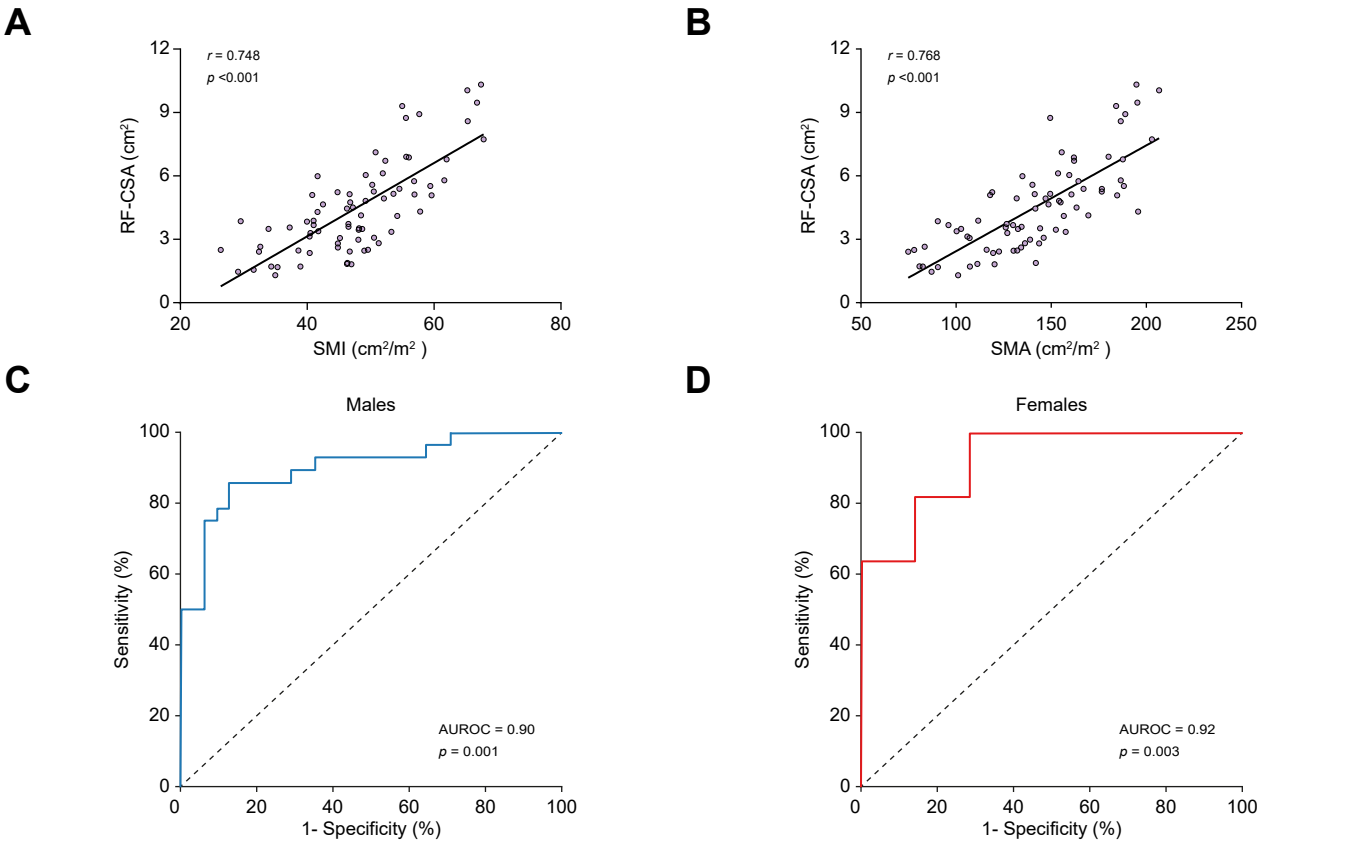

Fig. 2. Correlation of RF-CSA with SMI and SMA and discrimination ability for sarcopenia. Correlation between (A) SMI and RF-CSA and (B) SMA and RF-CSA, assessed using Pearson's correlation coefficient. (C,D) Discrimination ability of RF-CSA for ruling out sarcopenia in (C) men and (D) women. The endpoint of these curves was the absence of sarcopenia. Discrimination ability was evaluated using the AUROC. RF-CSA, rectus femoris cross-sectional area; SMA, skeletal muscle area; SMI, skeletal muscle index.

liver function, as shown by higher MELD score (18 *vs.* 15; p = 0.022) and higher prevalence of ascites (87% *vs.* 54%; p = 0.004). Patients with sarcopenia had a lower BMI and MAMC and a higher LFI compared with those without sarcopenia. RF-CSA was significantly lower in patients with than in those without sarcopenia (3.5 *vs.* 5.4 cm^2; p <0.001). Patients with sarcopenia were more frequently at risk of malnutrition, as shown by higher RFH-NPT score. In multivariable analysis (adjusted for age, MELD score, BMI, and MAMC), RF-CSA was independently associated with sarcopenia (OR = 0.27; p <0.001) along with sex (OR = 0.02; , <0.001) (Table S3). RF-CSA showed a high discrimination ability for ruling out sarcopenia (AUROC = 0.90 in men and 0.92 in women; Fig. 2C,D). The optimal threshold was 4.87 cm^2 for men (sensitivity = 86%; specificity = 84%) and 2.42 cm^2 for women (sensitivity = 82%; specificity 86%). The thresholds remained accurate in patients with or without obesity (sensitivity = 87% *vs.* 86%; specificity = 89% *vs.* 81%, respectively).

Phase 2

Study population

After demonstrating that RF-CSA is a reliable measure of muscle mass, we evaluated its prognostic ability in phase 2. During the study period, we screened 324 patients with cirrhosis admitted to hospital. Of these, 121 were excluded for different reasons (Fig. S1); therefore, 203 patients were enrolled. Of these enrolled patients, 84 (41%) had never previously experienced decompensation, 119 (59%) had a further decompensation, and none had achieved recompensation before the index hospitalization. The characteristics of the study population are reported in Table 2. Most patients were men (144 patients, 71%) and had alcoholic (58%) or metabolic (23%) cirrhosis. The mean age was 64 ± 10 years and 114 were overweight or obese. At inclusion, the median biochemical MELD score was 17 (IQR 13–23). Out of 203 patients, 148 (73%) had ascites and 65 (32%) HE. The median value of RF-CSA was 3.1 cm^2 (IQR 2.4–4.2). We used the convex transducer for the RF-CSA measurement in only 10 patients.

Complications during hospitalization

At admission, 99 patients had infections (49%), 61 presented with AKI (30%), 65 with HE (32%), 16 with shock (8%), and 44 with ACLF (22%). During their hospital stay, 23 patients developed infections (11%), 50 sepsis (25%), 30 AKI (15%), 20 HE (10%), 22 shock (11%), and 33 ACLF (16%); of all patients, 19 were transferred to the ICU at a median time of 15 days (IQR 3–25.5) after the admission, eight required RRT and 14 MV. When considering both events present at admission and those that developed during hospitalization, median

Table 2. Baseline characteristics of patients enrolled in phase 2.

Variable	All patients (n = 203)
Sex, female; n (%)	59 (29)
Age, years; mean (SD)	64 (10)
Ethnicity; n (%)	
White	199 (98)
Black	1 (0.5)
Asian	3 (1.5)
Etiology; n (%)	
Alcohol	117 (58)
HCV	40 (20)
HBV	21 (10)
MASLD	46 (23)
Other	43 (21)
First AD; n (%)	84 (41)
HCC; n (%)	38 (19)
Diabetes; n (%)	86 (42)
Overweight/obese; n (%)	114 (56)
MAP, mmHg; median (IQR)	80 (73–87)
WBCs, x10^9/L; median (IQR)	5.5 (3.5–8.0)
Hemoglobin, g/dl; median (IQR)	9.9 (8.9–11.3)
Platelets, x10^9/L; median (IQR)	87 (54–125)
INR; median (IQR)	1.5 (1.3–1.8)
Creatinine, μmol/L; median (IQR)	89 (65–126)
Sodium, mmol/L; median (IQR)	136 (134–138)
Bilirubin, μmol/L;median (IQR)	44 (25–115)
Albumin, g/L; median (IQR)	30 (27–33)
CRP, mg/L; median (IQR)	20 (8-45)
Ascites; n (%)	148 (73)
HE; n (%)	65 (32)
Ongoing infection; n (%)	99 (49)
AKI; n (%)	61 (30)
ACLF; n (%)	44 (22)
MELD score; median (IQR)	17 (13–23)
Child-Pugh score; median (IQR)	9 (8–11)
RFH-NPT score; median (IQR)	3 (2–5)
MAMC, cm; median (IQR)	23 (20–25)
RF-CSA, cm^2; median (IQR)	3.1 (2.4–4.2)

ACLF, acute-on-chronic liver failure; AD, acute decompensation; AKI, acute kidney injury; CRP, C reactive protein; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; INR, international normalized ratio; MAMC, mid-arm muscle circumference; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; RF-CSA, rectus femoris cross-sectional area; RFH-NPT, Royal Free Hospital-Nutritional Prioritizing Tool; WBCs, white blood cells.

values of RF-CSA were significantly lower in those patients who developed AKI, HE, sepsis, shock, and ACLF and had need of RRT than in those who did not (Fig. 3). In the multivariable analysis (adjusted for age, sex, and MELD), RF-CSA was an independent predictor of sepsis (OR = 0.59; 95% CI = 0.42–0.80; p = 0.001), AKI (OR = 0.75; 95% CI = 0.59–0.95; p = 0.019), HE (OR = 0.78; 95% CI = 0.62-0.96; p = 0.023), and shock (OR = 0.60; 95% CI = 0.40–0.84; p = 0.005) (Table 3).

In-hospital mortality

During their hospital stay, 32 patients died (16%), seven patients underwent LT (3%), and 164 patients survived (81%). In the univariable analysis**,** patients who died during hospitalization had a higher prevalence of ongoing infections (84 *vs.* 41%; p <0.001) and ACLF (44 *vs*15%; p = 0.001), and more severe AKI stage (Table S4). Patients who died showed higher levels of white blood cells (WBCs), international normalized ratio (INR), bilirubin, and C reactive protein (CRP), and higher scores of liver disease severity. RF-CSA was significantly lower in patients who died than in those who survived hospitalization (2.6 (IQR = 1.8–3.2) *vs.* 3.2 (IQR = 2.4–4.3) cm^2; p = 0.005). Stratification in tertiles of RF-CSA, calculated for men (lower tertile RF-CSA <2.87 cm^2; intermediate tertile 2.87 ≤RF-CSA <4.15 cm^2; higher tertile RF-CSA ≥4.15 cm^2) and for women (lower tertile RF-CSA <1.86 cm^2; intermediate tertile 1.86 ≤RF-CSA <2.97 cm^2; higher tertile RF-CSA ≥2.97 cm^2), confirmed that those with higher RF-CSA had lower in-hospital mortality. In the multivariable model (adjusted for age, sex, MELD score, infections, and RF-CSA, the latter considered a continuous variable), MELD score (OR = 1.18; 95% CI = 1.09–1.27; p <0.001) and infections (OR = 5.00; 95% CI = 1.72–14.51; p = 0.003) were independent predictors of in-hospital mortality (Table S5, model 1), whereas RF-CSA was associated with a lower risk of death, although it did not reach the level of significance (OR = 0.68; 95% CI = 0.46–1.00; p = 0.051). In model 2 (using ACLF instead of MELD score), ACLF was independently associated with in-hospital mortality (OR = 3.17, 95% CI = 1.29–7.79; p = 0.011) alongside infections.

90-day mortality

During the 90-day follow-up, 53 patients died (26%), 18 patients underwent LT (9%), and 12 patients were lost to follow-up (7%). The univariable analysis of factors associated with 90-day mortality is shown in Table S6. Among the clinical and laboratory variables, risk factors for 90-day mortality were ongoing infections, worse liver and renal function tests (as shown by INR, bilirubin, creatinine and MELD score), and higher levels of WBCs, ACLF, and AKI. In addition, lower muscle mass, as shown by RF-CSA (sHR = 0.60; 95% CI = 0.43–0.82; p = 0.002) and MAMC and higher risk of malnutrition, as shown by RFH-NPT score, were associated with higher risk of 90-day mortality. In patients without ACLF (n = 159), lower RF-CSA was significantly associated with 90-day mortality (sHR = 0.63; 95% CI = 0.46–0.85; p = 0.003). In patients with ACLF (n = 44), lower RF-CSA was associated with 90-day mortality, but it did not reach statistical significance (sHR = 0.69; sHR = 0.45–1.04; p = 0.073). In patients without obesity (n = 164), lower RF-CSA was significantly associated with 90-day mortality (sHR = 0.64; 95% CI = 0.48–0.84; p = 0.002). In patients with obesity (n = 35), lower RF-CSA was also associated with 90-day mortality, but the association did not reach statistical significance (sHR = 0.64; 95% CI = 0.38–1.09; p = 0.099).

In the multivariable analysis (adjusted for age, sex, MELD, and infections), low RF-CSA was an independent predictor of 90-day mortality (sHR = 0.57; 95% CI = 0.38–0.85; p = 0.006), along with MELD score (sHR = 1.11; 95% CI = 1.07–1.16; p <0.001) (Table 4, model 1). Even after adjusting for ACLF, low RF-CSA was associated with 90-day mortality (sHR = 0.66; 95% CI = 0.49–0.90; p = 0.008; Table 4, model 2). Figure 4 shows the cumulative incidence of 90-day mortality according to RF-CSA tertiles. There was a stepwise increase in the cumulative incidence of 90-day mortality when moving from the higher to the lower tertile.

Furthermore, by stratifying patients into two groups according to the RF-CSA thresholds for sarcopenia identified in phase 1 (4.87 cm^2 for men and 2.42 cm^2 for women), the cumulative incidence of 90-day mortality was significantly higher in patients with RF-CSA below the threshold than those with RF-CSA at or above the threshold (33.1% *vs.* 13.1%,

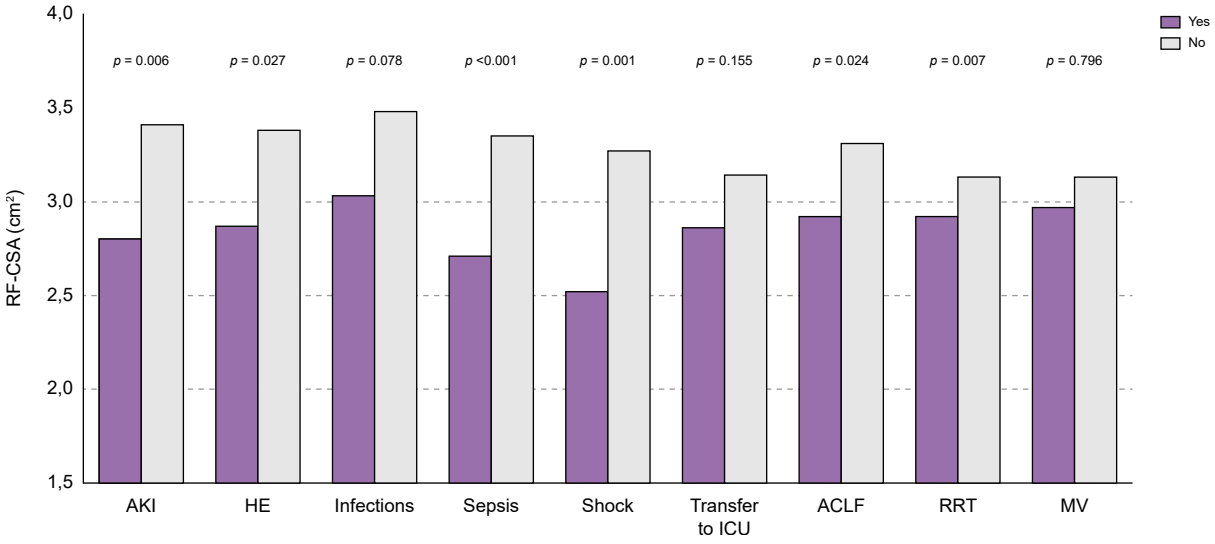

Fig. 3. Median values of RF-CSA in patients who did or did not develop complications during their hospital stay. RF-CSA values reported as medians, comparisons made with the Mann-Whitney *U* test. ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; HE, hepatic encephalopathy; ICU, intensive care unit; MV, mechanical ventilation; RF-CSA, rectus femoris cross-sectional area; RRT, renal replacement therapy.

Table 3. Association of RF-CSA with the risk of infection, sepsis, AKI, overt HE, shock, ACLF, transfer to ICU, need for RRT, and need for MV during hospitalization.

Variable	OR (95% CI)	*p* value
Infection	0.91 (0.73–1.12)	0.356
Sepsis	0.59 (0.42–0.80)	0.001
AKI	0.75 (0.59–0.95)	0.019
HE	0.78 (0.62–0.96)	0.023
Shock	0.60 (0.40–0.84)	0.005
ACLF	0.79 (0.60–1.03)	0.088
Transfer to ICU	0.74 (0.48–1.06)	0.134
Need for RRT	0.53 (0.23–1.01)	0.098
Need for MV	0.81 (0.51–1.20)	0.343

A logistic regression model adjusted for age, sex, and MELD score was used to determine the level of association. ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; HE, hepatic encephalopathy; ICU, intensive care unit; MV, mechanical ventilation; OR, odds ratio; RF-CSA, rectus femoris cross-sectional area; RRT, renal replacement therapy.

Table 4. Multivariable analysis of 90-day mortality.

Variable	sHR (95% CI)	*p* value
Model 1		
Age (years)	1.01 (0.98–1.04)	0.578
Sex (F *vs.* M)	0.93 (0.52–1.65)	0.803
MELD score	1.11 (1.07–1.16)	<0.001
Infections	1.37 (0.71–2.61)	0.346
RF-CSA (cm^2)	0.57 (0.38–0.85)	0.006
Model 2		
Age (years)	0.99 (0.97–1.01)	0.410
Sex (F *vs.* M)	1.07 (0.64–1.82)	0.790
ACLF	2.29 (1.33–3.94)	0.003
Infections	1.82 (1.05–3.15)	0.034
RF-CSA (cm^2)	0.66 (0.49–0.90)	0.008

Multivariable analysis was performed using the Fine-Gray subdistribution hazard model; LT was considered a competing risk for mortality. ACLF, acute-on-chronic liver failure; LT, liver transplantation; MELD, model for end-stage liver disease; RF-CSA, rectus femoris cross sectional area; sHR, subdistribution hazard ratio.

respectively; $p = 0.005$) (Fig. S2). We categorized patients according to MELD score >17 and ≤17 and RF-CSA thresholds and found worse prognosis in those with lower RF-CSA in both groups (Fig. S3).

Intra and inter-rater reliability

Intra- and inter-rater reliability was excellent (intraclass correlation coefficient [ICC] = 0.980 and 0.947, respectively, p <0.001 for both).

The time to obtain a RF-CSA was recorded in 10 patients and the mean time was 60.83 ± 21.8 s. Time required to perform the measurement decreased from the first to the third one (mean time for the first, 90.17 s; second, 50.68 s; and third, 42.40 s). We did not encounter technical limitations when performing the RF-CSA measurements in patients with low extremity edema (n = 74).

Discussion

Sarcopenia is highly prevalent in patients with cirrhosis and is linked to poor clinical outcomes. Currently, CT imaging is considered the gold standard for assessing muscle mass; however, this technique presents several drawbacks and limited application in daily clinical practice because of high costs, X-ray exposure, and the need for specific software.

In this study, we demonstrated the accuracy and reliability of RF ultrasound for assessing sarcopenia in cirrhosis. Our first original finding is that RF-CSA was strongly correlated with SMI at L3 and showed a high discrimination ability for sarcopenia in both men and women. Other studies have explored the use of ultrasound of thigh and/or the upper arm for evaluating sarcopenia in patients with cirrhosis, with controversial results.[14,15] In these studies, ultrasound was applied to measure the muscle thickness of the thigh or the upper arm. Although a significant correlation was found between muscle thickness and SMI, the power of correlation was weak, and applicability limited. These weak correlations between muscle thickness measured with ultrasound and muscle mass measured with CT scan and MRI have also been shown in other fields, such as geriatric medicine, where RF-CSA and gastrocnemius CSA showed a higher correlation with muscle mass.[21] RF-CSA has been applied in several

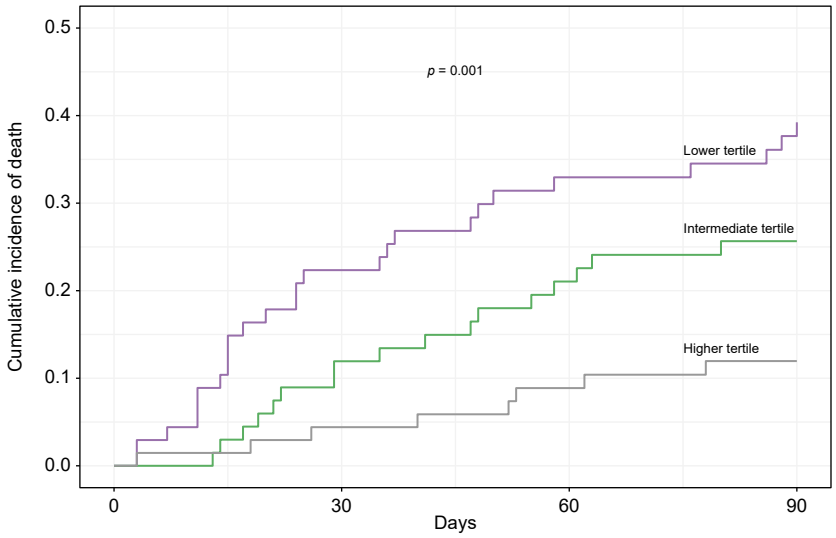

Fig. 4. Cumulative incidence of 90-day mortality according to tertiles of RF-CSA. Cumulative incidence function of 90-day mortality developed through competing risks analysis and compared with Gray's test. tertiles were calculated for men (lower tertile RF-CSA <2.87 cm^2; intermediate tertile 2.87 ≤RF-CSA <4.15 cm^2; higher tertile RF-CSA ≥4.15 cm^2) and for women (lower tertile RF-CSA <1.86 cm^2; intermediate tertile 1.86≤ RF-CSA <2.97 cm^2; higher tertile RF-CSA ≥ 2.97 cm^2). RF-CSA, rectus femoris cross sectional area.

other settings, such as critical care,[12] surgery,[18] nephrology,[22] and pneumology,[13] with excellent results. Herein, we applied this method for the first time to patients with cirrhosis, showing that, even in this population, RF-CSA is highly reliable. Importantly, the measurement of RF-CSA showed excellent intra- and inter-rater reliability, a strong correlation with functional parameters, and a better correlation with SMI compared with muscle thickness. Moreover, ultrasound measurements can be affected by probe pressure, which has been evaluated mainly for muscle thickness,[14] while CSA assessments are usually performed with no or minimal pressure.[18,23] To minimize bias, all RF-CSA measurements in our study were conducted without compression, following standardized protocols for anatomical landmarks, probe positioning, and image evaluation. This approach reduces operator variability and compression-related distortion, thereby enhancing reproducibility and supporting the use of RF-CSA as a reliable tool for muscle assessment. Furthermore, the ultrasound assessment was quick to perform, with average procedure times of just a few minutes, and was also easy to learn. Moreover, in line with the available literature, the intra and inter-rater variabilities were very low, making the tool highly reliable.[10] Therefore, the ultrasound assessment of RF-CSA can be used as a point-of-care examination for assessing sarcopenia in patients with cirrhosis.

Thus, RF-CSA could be used as a screening tool for sarcopenia and be combined with the assessment of risk of malnutrition. In fact, several patients in our cohort were at risk of malnutrition according to the RFH-NPT. Identifying patients at increased risk of malnutrition allows an appropriate nutritional strategy to be implemented, especially in patients hospitalized for AD of the disease.

A second relevant result of this study was the link between low RF-CSA and the occurrence of sepsis, shock, HE, and AKI during hospitalization. In addition, low RF-CSA values were associated with an increased risk of in-hospital and 90-day mortality. While sarcopenia has been clearly associated with poor outcomes,[2,24–26] only a few smaller studies have demonstrated the association of other ultrasound parameters with clinical outcomes in patients with cirrhosis. Hari *et al.* demonstrated the correlation between the ultrasound psoas muscle diameter with further decompensation and risk of mortality in decompensated cirrhosis, while the prospective study of Ciocîrlan *et al.* demonstrated that rectus abdominis thickness predicted survival.[27,28] More recently, Gödiker *et al.* found that the muscle thickness of quadriceps femoris measured by ultrasound was associated with decompensation in 63 patients with cirrhosis.[29]

Although sarcopenia is usually determined as a binary variable, muscle mass is a continuous variable, and the severity of muscle loss can correlate with clinical outcomes. This is why we used RF-CSA as a continuous variable for determining its association with clinical outcomes. Interestingly, we observed that the severity of muscle loss correlated with worsening of outcomes and increasing of mortality, as also shown by the stratification of RF-CSA in tertiles. This underscores the importance of the assessment of sarcopenia and muscle mass as a continuous variable rather than a binary outcome. In this regard, the use of thigh ultrasound, being rapid, easy, and low cost, can be used for repeated assessment of muscle mass. Indeed, it has been shown that the dynamic assessment of sarcopenia can enhance its prognostic value,[30] and ultrasound would allow repeated assessment of muscle mass, being easily performed even in outpatients. This could be easily applied to patients undergoing biannual abdominal ultrasound screening for HCC. In addition, ultrasound assessment could also be explored in candidates on the transplant waiting list, where sarcopenia is known to be associated with increased waitlist mortality.[3,4] Finally, RF-CSA changes could be explored as a surrogate outcome to assess nutritional/exercise intervention aiming at counteracting muscle loss in cirrhosis.

The strengths of our study include the use of the gold standard reference for assessing muscle mass (SMI) to evaluate the reliability of RF-CSA as an index of muscle mass/sarcopenia, and its validation in a large prospective cohort.

However, we acknowledge that the study has limitations. First, it is based on single-center data and, although the findings are consistent with those in other fields of medicine, external validation might still be necessary. In addition, we primarily assessed sarcopenia based on muscle mass, without evaluating thigh muscle strength. Another limitation is that RF-CSA is not able to capture myosteatosis, which has relevant prognostic implications in cirrhosis.[31] We recognize that the proportion of patients with HCC in phase 1 was relatively high, primarily because of the inclusion criteria used (abdominal CT scan for liver nodule characterization or LT evaluation), leading to a naturally higher prevalence of HCC. This introduces a potential limitation, given that patients with and without HCC differ prognostically. To reduce this potential bias, we excluded patients with HCC beyond the Milan criteria in both phases. Another limitation is the lack of ethnic diversity, with a predominantly White study population, which might limit the generalizability of our findings. Given that muscle mass and body composition vary across populations, further studies are needed to validate the predictive value of RF-CSA in more diverse cohorts. Furthermore, sarcopenia often manifests as site-specific muscle loss, particularly in the quadriceps and abdominal muscles, suggesting differences between appendicular and trunk regions, as shown by Abe *et al.*[32] In phase 1, we assessed rectus femoris muscle mass via ultrasound and compared it with CT-based evaluation of abdominal and paraspinal muscles, thus including both appendicular and trunk musculature. This methodological approach could introduce limitations, because the site-specific nature of muscle loss could affect comparability. In addition, the relatively short follow-up period restricts our assessment to short-term outcomes. Future studies with longer follow-up periods are needed to evaluate long-term functional outcomes, quality of life, and post-transplant recovery. Finally, although our analyses were adjusted to account for clinically meaningful confounders, the possibility of residual confounding factors cannot be entirely ruled out. For example, some factors, such as prolonged hospitalization, inadequate nutritional support, or specific nutritional interventions, could act as confounding factors affecting muscle status. However, addressing these influences would require dynamic assessment of muscle mass throughout the hospital stay, an approach that warrants consideration in future studies.

Despite these limitations, the results of this study underline the applicability of RF-CSA assessment by thigh ultrasound as a point-of-care tool for assessing sarcopenia in patients with decompensated cirrhosis. The assessment of RF-CSA is easy, reliable, safe, low cost, and repeatable and is associated with complications of cirrhosis and mortality in patients with AD.

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Abbreviations

ACLF, acute-on-chronic liver failure; AD, acute decompensation; AKI, acute kidney injury; BIA, bioelectrical impedance analysis; CT, computed tomography; CRP, C reactive protein; CSA, cross-sectional area; DXA, dual-energy X-ray absorptiometry; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HR, hazard ratio; ICC, intraclass correlation coefficient; ICU, intensive care unit; INR, international normalized ratio; LFI, Liver Frailty Index; LT, liver transplant; MAMC, mid-arm muscle circumference; MAP, mean arterial pressure; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; MV, mechanical ventilation; OR, odds ratio; RF-CSA, rectus femoris cross sectional area; RFH-NPT, Royal Free Hospital-Nutritional Prioritizing Tool; RRT, renal replacement therapy; sHR, subdistribution hazard ratio; SMA, skeletal muscle area; SMI, skeletal muscle index; WBCs, white blood cells

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Conflicts of interest

MT received travel support from Gilead and Grifols. PA received grant/research support from Grifols and CSL Behring; held a patent with Biovie; and served as a consultant for Sequana Medical. SP served as a consultant for Plasma Protein Therapeutics Association, Boehringer Ingelheim, and Resolution Therapeutics; and received speaker fees from Grifols, Ferring, and Medscape. The other authors have nothing to disclose related to the content of the manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design; study supervision: SP. Data collection: RG, PC, SB, SI, VC, BS, CGG. Statistical analysis: AB. Drafting of the manuscript: SP, RG. Revision for important intellectual content and approval of the final manuscript: all authors.

Data availability

Data related to this study will be made available by the corresponding author upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101564.

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Author names in bold designate shared co-first authorship

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