Journal of Clinical and Translational Research 2022; 8(3): 200-208

Journal of Clinical and Translational Research

Journal homepage: http://www.jctres.com/en/home

ORIGINAL ARTICLE

# Sarcopenia is the independent predictor of mortality in critically ill patients with cirrhosis

Saniya Khan[1†], Jaya Benjamin[1†*], Rakhi Maiwall[2], Harshita Tripathi[1], Puja Bhatia Kapoor[1], Varsha Shasthry[1], Vandana Saluja[3], Prashant Agrawal[3], Shalini Thapar[4], Guresh Kumar[5]

*[1]Department of Clinical Nutrition, Institute of Liver and Biliary Sciences, New Delhi, India, [2]Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India, [3]Department of Anesthesia and Critical Care, Institute of Liver and Biliary Sciences, New Delhi, India, [4]Department of Radiodiagnosis, Institute of Liver and Biliary Sciences, New Delhi, India, [5]Department of Clinical Research, Institute of Liver and Biliary Sciences, New Delhi, India*

*[†]These authors contributed equally to this work*

ARTICLE INFO

*Article history:*
Received: February 03, 2022
Revised: March 22, 2022
Accepted: April 01, 2022
Published online: May 25, 2022

*Keywords:*
body composition by computed tomography
mortality
nutrition in liver cirrhosis
sarcopenia
sepsis in intensive care unit

**Corresponding author:*
Jaya Benjamin
Department of Clinical Nutrition, Institute of Biliary Sciences, New Delhi, India.
Tel: +91-9540951081
E-mail: jayabenjaminilbs@gmail.com



ABSTRACT

**Background:** Sarcopenia is strongly associated with poor outcome in cirrhosis. There are little prospective data that sarcopenia influences outcomes in critically ill cirrhotics (CICs). Computed tomography (CT) is the gold standard for sarcopenia assessment in the intensive care unit (ICU), as it is independent of hydration status.

**Aim:** This study aims to assess the prevalence of sarcopenia and study its impact on clinical outcomes in CICs.

**Methods:** In this prospective observational study, CICs admitted to the liver ICU were enrolled, if meeting inclusion (age 18–70 years, abdominal CT scan within three months before ICU admission) and exclusion criteria (survival likely to be <24 h, coexisting chronic diseases). Clinical, hemodynamic, biochemical, and nutritional parameters, including length of stay (LOS), duration of mechanical ventilation (MV), development of new-onset infections (NOI), incidence of new-onset acute kidney injury (AKI), and overall survival, were recorded. CT images at the L3 level were analyzed using Slice-O-Matic V4.3 software to assess the skeletal muscle index (SMI) expressed as skeletal muscle area ($cm^2$)/height ($m^2$). Sarcopenia was defined if SMI was <50 $cm^2/m^2$ – males and <39 $cm^2/m^2$ – females. Data were analyzed using SPSS version 22.

**Results:** Altogether 111 patients (M-83.8%; age 48.4±11.3 years; etiology: Alcohol – 56 [50.5%], non-alcoholic steatohepatitis – 27 [24.3%], viral – 12 [10.8%], and others – 16 [14.4%]; Child-Turcotte-Pugh – 11.9±1.8; model for end-stage liver disease – 27.8±7.3; sequential organ failure assessment – 10.5±4.1; APACHE – 23±8; and MV – 54 [48.6%]) were enrolled. Of these, 76 (68.5%) were sarcopenic and 35 (31.5%) non-sarcopenic. Sarcopenic CICs had higher overall mortality (72.4%) compared to non-sarcopenics (40%) ($P$=0.001, OR [95% CI] – 3.93 [1.69–9.12]), and higher prevalence of sepsis at ICU admission (53.9% vs. 31.4%, $P$=0.027, OR [95% CI] – 1.7 [1.0–2.92]) than non-sarcopenics. LOS, duration of MV, incidence of NOI, and development of new-onset AKI were comparable between groups. Multivariate binary logistic regression showed that sarcopenia, sepsis, and APACHE II score were independently associated with mortality.

**Conclusion:** Two-thirds of CICs have sarcopenia at ICU admission, making them 1.7 times more susceptible to sepsis and increasing the risk of mortality by almost 4-fold in the ICU.

**Relevance for Patients:** Almost 70% of patients with chronic liver disease admitted to the ICU have low muscle mass (sarcopenia). The presence of sarcopenia *per se* makes them highly prone to infections and increases the chances of death by almost 4-fold; thus, highlighting the importance of nutrition optimization in this patient group.

DOI: http://dx.doi.org/10.18053/jctres.08.202203.006

## 1. Introduction

Chronic liver disease (CLD) is a progressive disorder that adds significantly to the global burden of disease. Nevertheless, over the past years, various supportive therapies and interventions have been introduced that have improved the clinical outcome of these patients, resulting in a significant increase in patient longevity. However, very often these patients face life-threatening complications such as variceal bleed, hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatopulmonary syndrome (HPS), and infections that necessitate intensive care unit (ICU) admission [1].

Malnutrition is yet another complication in CLD which has been described as the phenotype of skeletal muscle loss with or without loss of fat mass [2]. Likewise, it may also contribute significantly in determining the fate of critically ill cirrhotics (CICs). Loss of muscle mass termed as sarcopenia negatively impacts the overall outcome of the disease and is associated with increased mortality [3], impaired health-related quality of life [4], increased health-care cost [5], and poor liver transplant outcomes [6].

Even though nutritional assessment in the ICU is essential, it is very challenging. Moreover, the traditional markers of assessment often lose their specificity in CLD and critical illness [7]. Computed tomography (CT) has been considered the gold standard for assessing skeletal muscle mass [8], which is performed as a part of the routine investigation in these patients.

Sarcopenia has been associated with decreased ventilator-free days [9], difficulty in weaning [10], and increased mortality [11] in the general critically ill patients. In a retrospective study, rapid muscle decline was found to be associated with increased mortality in CICs also [12]. However, the impact of sarcopenia on the clinical outcomes, especially mortality in the CICs, has not been studied prospectively. Hence, we planned this study to assess the prevalence of sarcopenia in CICs at ICU admission and to gauge its impact on the clinical outcomes during the course of ICU stay.

## 2. Materials and Methods

### *2.1. Study population*

In this prospective observational study, 111 CICs, admitted to the liver ICU (LICU) of the Institute of Liver and Biliary Sciences, New Delhi, were enrolled from January 2020 to August 2020. The inclusion criteria were as follows: CICs of any etiology, age ≥ge years, and abdominal CT performed not more than 3 months before the LICU admission. Moribund patients and those with hepatocellular carcinoma or other malignancies were excluded from the study.

### *2.2. Study plan*

The work plan was to screen all the patients for eligibility. Baseline and daily follow-up information including demographic, clinical, hemodynamic, and biochemical details were gathered on a structured pro forma till the patient's stay in the ICU. The clinical outcomes of sarcopenics and non-sarcopenics were compared after muscle mass was evaluated and data were recorded on an Excel sheet.

### *2.3. Diagnosis of the disease*

Liver cirrhosis was diagnosed based on standard, clinical, biochemical, histological, and/or radiological criteria [13].

Acute-on-chronic liver failure (ACLF) was diagnosed using Asian Pacific Association for the Study of the Liver criteria [14].

### *2.4. Assessment of disease severity*

The severity of liver disease was assessed according to Child-Turcotte-Pugh (CTP) and Model for End-stage Liver Disease (MELD) scores. Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) scores were used to determine the severity of critical illness.

### *2.5. Assessment of sarcopenia*

All CT scans were performed on a Discovery 750 HD 64-row spectral CT scanner (GE, USA). A transverse CT image from the third lumbar vertebrae (L3) was identified from each scan. The CT images were analyzed using Slice-O-Matic software V4.3 (Tomovision, Montreal, Canada). The skeletal muscle area (SMA, in $cm^2$) was defined as the sum of the paraspinal, psoas, transversus abdominis, interior/exterior oblique, and rectus abdominis muscles at the level of L3 region. The identification of skeletal muscle was based on a predefined CT density of −29 to +150 Hounsfield Unit (HU) (Figure 1) [15]. The SMA was then normalized for stature (height in $m^2$) and expressed as skeletal muscle index (SMI) in $cm^2/m^2$. Sarcopenia was defined if SMI was <50 $cm/m^2$ in males and <39 $cm/m^2$ in females [16].

Bilateral psoas muscle attenuation was expressed in HU and measured using Picture Archiving and Communication System imaging software. An oval region of interest of 1.5 $cm^2$ was placed in the most homogenous area of the psoas muscle (Figure 2) and skeletal muscle density (SMD) was expressed as the mean of radiological muscle attenuation of both psoas muscles [17].

### *2.6. Medical management*

All the CICs admitted to the LICU were managed as per the standard guidelines including nutritional support, endotracheal intubation, fluid resuscitation, and renal replacement therapy

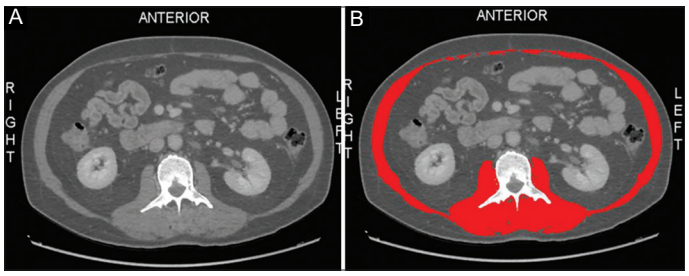


**Figure 1.** Computed tomography images used for the assessment of skeletal muscle mass. (A) Single-slice computed tomography image at L3. (B) Analyzed image in the Slice-O-Matic software. Red color indicates muscle (SMA).

DOI: http://dx.doi.org/10.18053/jctres.08.202203.006

(RRT). All the patients were screened for infection and treated empirically with broad-spectrum antibiotic combinations as per the treating ICU team.

### *2.7. Objective*

The primary objective was to assess the prevalence of sarcopenia at ICU admission and study its impact on the overall ICU mortality in critically ill patients with cirrhosis. The secondary objective was to study the effect of sarcopenia on other clinical outcomes such as duration of mechanical ventilation (MV), length of ICU stay, prevalence of sepsis, incidence of new-onset infections (NOI), development of new-onset acute kidney injury (AKI), and feed intolerance.

### *2.8. Data collection*

Apart from the routine baseline demographics, information was collected on duration in hospital prior to ICU admission; presence of comorbidities; decompensation status like ascites, jaundice, upper gastrointestinal bleed; presence of sepsis; reason of ICU admission including altered sensorium, respiratory distress, or metabolic acidosis; and disease severity scores including SOFA, APACHE II, CTP, and MELD scores. Follow-up data collected daily until the death or discharge of the patients included the hemodynamic parameters such as heart rate, mean arterial pressure, and requirement of vasopressors; biochemical parameters such as complete blood count, liver function test, kidney function test, coagulation factors, and random blood sugars; blood gas parameters such as pH, $PaO_2$, and $FiO_2$; and incidence of AKI, requirement of RRT, days of MV, development of NOI, and duration of ICU stay.

### *2.9. Definition of outcome variables*

#### 2.9.1. Length of ICU stay

It was considered from the day of admission to the ICU till discharge/shift-out from the ICU or death.

#### 2.9.2. Duration of MV

It was counted from the day of intubation till the day of extubation or death.

#### 2.9.3. Identification of sepsis

Microbiologically proven or presence of any one of the following – lung infiltrates, spontaneous bacterial empyema, SBP, cellulitis, urinary tract infection, or infection at the surgical site [18].

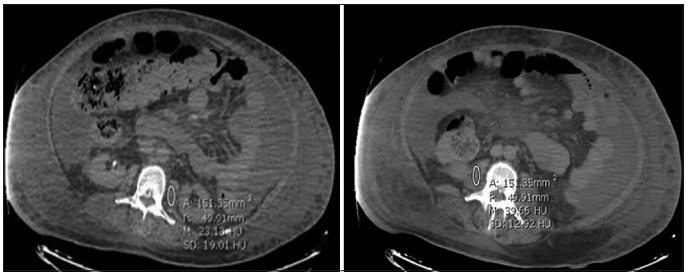

**Figure 2.** Computed tomography images used for the assessment of skeletal muscle density of the psoas muscle.

#### 2.9.4. New-onset infections

Development of new infection manifesting as pneumonia on X-ray, positive blood or mini-BAL culture reports or line sepsis during the stay in ICU after 48 h of admission [19].

#### 2.9.5. Acute kidney failure

The KDIGO has recommended a staging system for the severity of the AKI [20].

#### 2.9.6. Requirement of RRT

The requirement of RRT for the patients was assessed if the patient was on sustained low-efficiency dialysis or on continuous RRT (CRRT) [21].

#### 2.9.7. Incidence of feed intolerance

Feed intolerance was defined in terms of gastric residual volume >500 ml over 6 h [22].

#### 2.9.8. Mortality

Death in the ICU is taken as ICU mortality. The day of death was also noted to assess the time to death in the ICU.

### *2.10. Ethical clearance*

The study was approved by the Institutional Ethics Committee/ Institutional Review Board. (No F25/5/107/ILBS/AC/2016/11252/ DOA/151).

### *2.11. Statistical analysis*

Data were analyzed in SPSS version 22 and presented as mean (±standard deviation), median (range), or number (%) as appropriate. All variables were checked for normal distribution by Kolmogorov–Smirnov test and variables which did not follow normal distribution were analyzed using non-parametric methods. Continuous variables were compared between sarcopenics and non-sarcopenics using Student's t-test or Mann–Whitney as appropriate, and categorical variables were tested by Pearson Chi-square test or Fisher's exact test. Factors associated with mortality were ascertained by univariate and multivariate binary logistic regression analysis. $P<0.05$ was considered statistically significant.

## 3. Results

### *3.1. Baseline demographic and clinical characteristics of patients*

Of the 111 patients enrolled, the majority were male (83.8%) with a mean age of 48.4±11.3 years. The cohort included 82.9% of patients with CLD and 17.1% with ACLF, in whom the most common etiology was alcohol-associated cirrhosis in 50.5% and comorbidities were present in 45.9%. The patients had a mean body mass index (BMI) of 24 kg/m$^2$, with 92.3% having Child C status, with high MELD (27.87), SOFA (10.52), and APACHE II (23). The most common reason for ICU admission was HE (38.7%) (Table 1).

DOI: http://dx.doi.org/10.18053/jctres.08.202203.006

MV was required in 48.6% of patients, while 34.2% had shock and 46.8% had sepsis at ICU admission. AKI was present in 53.1% of the patients, although 22% required CRRT at ICU admission (Table 2). Baseline biochemical details of the CICs are summarized in Table 3.

### 3.2. Prevalence of sarcopenia

Of the 111 patients, 76 (68.5%) had sarcopenia with a mean SMA of 113.1 $cm^2$, SMI of 40.67 $cm^2/m^2$, and SMD of 50.58 HU which was significantly lower than those without sarcopenia. Sarcopenics had a significantly lower dry BMI at ICU admission and a significantly higher prevalence of sepsis (OR=1.7 [1.0–2.92]; *P*=0.027). All the other biochemical and clinical parameters were comparable between sarcopenics and non-sarcopenics (Tables 1-3).

### 3.3. Effect of sarcopenia on mortality

The overall ICU mortality was 69 (62.2%). Mortality among sarcopenics 55 (72.4%) was significantly higher (*P*=0.001) as compared to non-sarcopenic patients 14 (40%), OR (95% CI): 3.93 (1.69–9.12), suggesting almost 4 times higher risk of mortality among patients with sarcopenia. Of the 69 deaths, 53.6% mortality occurred at 7 days, 26.2% at 14 days, and 10.1% at 28 days. However, the Kaplan–Meier survival analysis did not reach statistical significance (*P*=0.138) as there was no significant difference in time to death (days) between sarcopenics and non-sarcopenics (Figure 3).

### 3.4. Effect of sarcopenia on other clinical variables during the ICU stay

As shown in Table 4, the length of ICU stay and duration of MV were comparable between the groups. Prevalence of sepsis at

**Table 1.** Baseline demographic and clinical characteristics of critically ill cirrhotics

| Variable | All (*n*=111) (%) | Sarcopenic (*n*=76) (%) | Non-sarcopenic (*n*=35) (%) | *P*-value |
|---|---|---|---|---|
| Age (years) | 48.37±11.29 | 48.49±11.5 | 48.11±10.9 | 0.873 |
| Gender | | | | |
| Male | 92 (83.8) | 65 (85.5) | 28 (80) | 0.463 |
| Female | 18 (16) | 11 (14.5) | 7 (20) | |
| Diagnosis | | | | |
| CLD | 92 (82.9) | 60 (78.9) | 32 (91.4) | 0.105 |
| ACLF | 19 (17.1) | 16 (21.1) | 3 (8.6) | |
| Etiology | | | | |
| Ethanol | 56 (50.5) | 40 (52.6) | 16 (45.7) | 0.094 |
| NASH | 27 (24.3) | 14 (18.4) | 13 (37.1) | |
| Viral | 12 (10.8) | 8 (10.5) | 4 (11.4) | |
| Others | 16 (14.4) | 14 (18.4) | 2 (5.7) | |
| Comorbidities | 51 (45.9) | 34 (44.7) | 17 (48.6) | 0.706 |
| Reason for admission | | | | |
| Hepatic encephalopathy | 67 (60.4) | 45 (59.2) | 22 (62.9) | 0.715 |
| Variceal bleed | 14 (12.6) | 7 (9.2) | 7 (20) | 0.112 |
| Respiratory distress | 33 (29.7) | 21 (27.6) | 12 (34.5) | 0.476 |
| Shock | 22 (19.8) | 16 (21.1) | 6 (17.1) | 0.631 |
| Others | 16 (14.4) | 11 (14.5) | 5 (14.3) | 0.979 |
| Presence of ascites | 68 (61.3) | 46 (60.5) | 22 (64.7) | 0.677 |
| Dry BMI ($kg/m^2$) | 24±4.32 | 22.9±3.7 | 26.3±4.6 | <0.001* |
| SMD | 51.82±9.77 | 50.58±10.22 | 54.52±8.22 | 0.033* |
| CTP score | 11.94±1.83 | 11.8±1.8 | 12.06±1.8 | 0.642 |
| Child B | 8 (7.2) | 7 (9.2) | 1 (2.9) | 0.229 |
| C | 103 (92.3) | 69 (90.8) | 34 (97.1) | |
| MELD score | 27.87±7.35 | 28.2±8.2 | 27.6±7.7 | 0.690 |
| SOFA score | 10.52±4.11 | 10.6±3.9 | 10.1±4.5 | 0.545 |
| APACHE II score | 23.04±8.03 | 23.6±7.9 | 21.6±8 | 0.231 |
| Sepsis at baseline | 52 (46.8) | 41 (53.9) | 11 (31.4) | 0.027* |
| Presence of AKI | 59 (53.1) | 43 (56.8) | 16 (45.7) | 0.286 |
| Requirement of RRT | 13 (22) | 9 (11.8) | 4 (11.4) | 0.950 |

Data are expressed as Mean±SD or number (%), *significant at *P*<0.05; CLD: Chronic liver disease; ACLF: Acute-on-chronic liver failure; NASH: Non-alcoholic steatohepatitis; BMI: Body mass index; SMD: Skeletal muscle density; CTP: Child-Turcotte-Pugh; MELD: Model for end-stage liver disease; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology, Age, Chronic Health Evaluation II; AKI: Acute kidney injury; RRT: Renal replacement therapy

DOI: http://dx.doi.org/10.18053/jctres.08.202203.006

**Table 2.** Baseline hemodynamic and arterial blood gas parameters of critically ill cirrhotics

| Variable | All (*n*=111) (%) | Sarcopenic (*n*=76) | Non- sarcopenic (*n*=35) | *P*-value |
|---|---|---|---|---|
| MAP (mmHg) | 64.60±12.4 | 87.3±15.6 | 86±11.7 | 0.662 |
| Shock | 38 (34.2) | 28 (36.8) | 10 (28.6) | 0.394 |
| Mechanical ventilation | 54 (48.6) | 39 (51.3) | 15 (42.9) | 0.407 |
| $FiO_2$ | 50 (10–100) | 47.5 (10–100) | 50 (21–100) | 0.702 |
| $PaO_2$ | 147.12±71.64 | 152.5±73.7 | 135.4±66.2 | 0.245 |
| $PaCO_2$ | 31.79±7.40 | 31.35±7.73 | 32.67±6.76 | 0.486 |
| pH | 7.39±0.10 | 7.2±0.24 | 7.3±0.27 | 0.203 |
| Lactate (mmol/L) | 2.15 (0.1–15.4) | 2.5 (0.1–15.4) | 2.1 (0.3–10.8) | 0.426 |

Data are expressed as Mean±SD or median (min-max) or number (%); MAP: Mean arterial pressure, $FiO_2$: Fraction of inspired oxygen; $PaO_2$: Partial pressure of oxygen, $PaCO_2$: Partial pressure of carbon dioxide.

**Table 3.** Baseline routine biochemical investigations of critically ill cirrhotics

| Variable | All (*n*=111) | Sarcopenic (*n*=76) | Non-sarcopenic (*n*=35) | *P*-value |
|---|---|---|---|---|
| Hemoglobin (g/dL) | 8.61±2.01 | 8.5±2.1 | 8.6±1.6 | 0.835 |
| TLC (cumm) | 8.9 (1–44.1) | 8.6 (0.9–37.5) | 9.3 (1.4–44.1) | 0.900 |
| Platelet (thousand) | 77 (17–378) | 84.5 (17–378) | 65 (18.9–201) | 0.172 |
| INR | 2 (0.86–11) | 2.17 (0.86–11) | 2.13 (1.3–4.03) | 0.610 |
| Urea (mg/dL) | 68.5 (7.7–337) | 70.6 (7.7–337) | 55.6 (10.7–207.5) | 0.186 |
| Creatinine (mg/dL) | 1.08 (0–10.92) | 1.25 (0.03–10.92) | 1.09 (0.30–4.49) | 0.921 |
| Sodium (mmol/L) | 133.93±6.67 | 133.7±6.7 | 134.3±6.6 | 0.688 |
| Potassium (mmol/L) | 4.35±1.02 | 4.4±1 | 4.3±0.93 | 0.892 |
| Calcium (mg/dl) | 8.41±0.91 | 8.5±0.98 | 8.2±0.75 | 0.089 |
| Magnesium (mg/dL) | 2.08±0.44 | 2.1±0.46 | 2.09±0.48 | 0.819 |
| Phosphorus (mg/dL) | 3.6 (1–10.3) | 3.5 (1.2–10.3) | 3 (1–6.1) | 0.628 |
| Total protein (g/dL) | 6.22±0.95 | 6±1.5 | 6.1±0.86 | 0.834 |
| Serum albumin (g/dL) | 2.56±0.54 | 2.3±0.47 | 2.6±0.59 | 0.005 |
| Total bilirubin (mg/dL) | 7.15 (0–46.3) | 8 (0.5–46.3) | 5 (0.9–37.9) | 0.464 |
| AST (IU/L) | 82 (22–1918) | 83 (22–1918) | 82 (38–437) | 0.567 |
| ALT (IU/L) | 44 (9–1449) | 38 (22–1449) | 53 (11–201) | 0.127 |
| Arterial ammonia (mmol/L) | 194 (50–596) | 194 (50–596) | 194.5 (62–494) | 0.880 |
| Random blood sugar (mg/dL) | 140±29.64 | 142±29.3 | 135.7±30.3 | 0.308 |

Data are expressed as Mean±SD or median (min-max); TLC: Total leukocyte count; INR: International normalized ratio; AST: Aspartate transaminase, ALT: Alanine aminotransferase

**Table 4.** Comparison of other clinical outcome parameters between sarcopenics and non-sarcopenics

| Variable | Sarcopenic (*n*=76) (%) | Non-sarcopenic (*n*=35) (%) | *P*-value |
|---|---|---|---|
| Length of ICU stay (days) | 5 (2–28) | 5 (2–22) | 0.860 |
| Duration of MV (days) | 5.5 (1–28) | 5.5 (1–22) | 0.731 |
| Sepsis foci | | | |
| Lung | 20 (50) | 5 (38.5) | 0.896 |
| SBP | 9 (22.5) | 2 (15.4) | |
| Blood culture | 5 (12.5) | 1 (7.7) | |
| Others | 6 (15) | 5 (38.5) | |
| New-onset infection | 27 (62.8) | 16 (37.2) | 0.306 |
| Incidence of feed intolerance during ICU stay | 22 (28.9) | 5 (14.3) | 0.094 |
| New-onset AKI | 7 (9.2) | 5 (14) | 0.546 |
| ICU mortality | 55 (72.4) | 14 (40) | 0.001* |

Data are expressed as median (min-max) or number (percentage), *significant at $P<0.05$; ICU: Intensive care unit; MV: Mechanical ventilation; SBP: Spontaneous bacterial peritonitis, AKI: Acute kidney injury

baseline was significantly higher ($P$=0.027) in sarcopenics (53.9%) as compared to non-sarcopenics (31.4%), with lungs being the most common foci. Sarcopenics had a trend toward a higher incidence of feed intolerance during ICU although it was not significant ($P$=0.094). The incidence of new-onset sepsis and AKI, and requirement of RRT was comparable between sarcopenics and non-sarcopenics.

In univariate analysis, the presence of shock ($P$=0.001), respiratory distress ($P$=0.02), sepsis ($P\leq$0.001), MV ($P\leq$0.001), and sarcopenia ($P$=0.001), total leukocyte count ($P$=0.027), hemoglobin ($P$=0.043), SOFA score ($P$=0.001), APACHE II score ($P\leq$0.001), CTP score ($P$=0.015), and MELD score ($P$=0.038) was associated with mortality, as shown in Table 5. However, on multivariate analysis, sarcopenia ($P$=0.002), sepsis ($P$=0.009), and APACHE II ($P$=0.032) score were found to be independently associated with mortality ($R^2$=0.394) (Table 5).

## 4. Discussion

Notwithstanding the huge advancements in medical therapies and salvage interventions, patients with liver cirrhosis do end up

DOI: http://dx.doi.org/10.18053/jctres.08.202203.006

**Table 5.** Independent factors associated with mortality in critically ill cirrhotics

| Variables | Univariate regression analysis | | Multivariate regression analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Age (years) | 1.02 (0.98–1.05) | 0.264 | | |
| Gender (M: F) | 0.58 (0.19–1.77) | 0.582 | | |
| Dry_BMI (kg/m$^2$) | 0.93 (0.84–1.02) | 0.124 | | |
| Shock | 8.16 (1.79–37.04) | <0.001 | | |
| Respiratory distress | 3.02 (1.17–7.78) | 0.022 | | |
| Variceal bleed | 0.56 (0.18–1.74) | 0.565 | | |
| Encephalopathy | 0.75 (0.34–1.65) | 0.488 | | |
| Sepsis | 7.48 (3.0–18.64) | <0.001 | 4.44 (1.63–12.08) | 0.003 |
| Mechanical ventilation | 0.145 (0.6–3.54) | <0.001 | | |
| Hemoglobin (g/dL) | 0.81 (0.66–0.99) | 0.043 | | |
| TLC (cumm) | 1.07 (1.0–1.14) | 0.027 | | |
| INR | 1.45 (0.97–2.14) | 0.064 | | |
| Sodium (mmol/L) | 1.04 (9.81–1.10) | 0.187 | | |
| Calcium (mg/dL) | 1.36 (0.88–2.09) | 0.163 | | |
| Albumin (g/dL) | 1.75 (0.86–3.56) | 0.118 | | |
| Total bilirubin (mg/dL) | 1.03 (0.99–1.07) | 0.081 | | |
| Lactate (mmol/L) | 1.08 (0.93–1.27) | 0.288 | | |
| Sarcopenia | 3.92 (1.69–9.12) | 0.001 | 3.50 (1.32–9.33) | 0.011 |
| SOFA score | 1.22 (1.09–1.37) | 0.001 | | |
| APACHE II score | 1.12 (1.06–1.18) | <0.001 | 1.09 (1.03–1.16) | 0.004 |
| CTP | 1.31 (1.05–1.65) | 0.015 | | |
| MELD | 1.05 (1.0–1.11) | 0.038 | | |

BMI: Body mass index; TLC: Total leukocyte count; INR: International normalized ratio; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology, Age, Chronic Health Evaluation II; CTP: Child-Turcotte-Pugh; MELD: Model for end-stage liver disease.

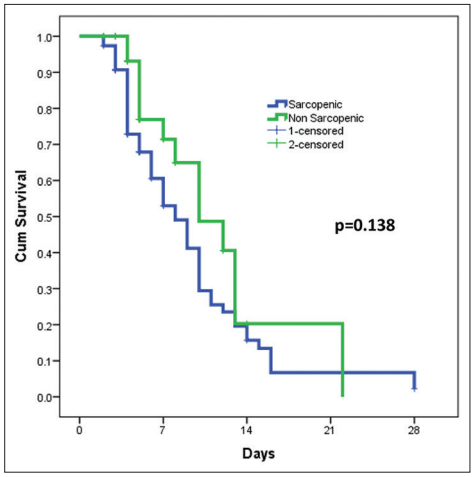


**Figure 3.** Kaplan–Meier survival curves for mortality of sarcopenic and non-sarcopenic.

developing life-threatening complications such as HE, variceal bleed, SBP, and HPS which require intensive medical care [1]. Loss of muscle mass or sarcopenia is also one of the major complications seen in patients with cirrhosis [2].We planned to study the effect of sarcopenia on the clinical outcomes of this select group of patients in the ICU [2]. To the best of our knowledge, this is the only study examining such an aspect in a very closed group of CICs.

Our study of 111 CICs including both decompensated cirrhotics and ACLF patients revealed a very high prevalence of sarcopenia at the time of ICU admission. We found that almost two-thirds of our patients had sarcopenia as defined by SMI studied with the help of CT scan images. We kept our study CT based as it is a widely studied method, which is free from hydration status. Moreover, CT scans are mostly available in the ICU setup. The muscle area assessed from a single-slice CT image has shown a good correlation with total body skeletal muscle quantified by multi-slice analysis [23].

A recent retrospective study found that 90.4% of CICs had sarcopenia at the time of ICU admission [12]. This figure is higher than any other study of critically ill patients, where prevalence ranges from 31% to 71% [9,10,24,25]. In patients with cirrhosis, particularly transplant waitlisted candidates, sarcopenia is present in almost 45% [26-29]. It is well known that cirrhotics have a higher prevalence of sarcopenia. We also found sarcopenia in 68.5% of CICs. This prevalence may be underestimated as we only included those patients in the study who had a CT scan within≤3 months of ICU admission. Despite that, we found that two in every three patients had sarcopenia. Hence, the true prevalence of sarcopenia may be much higher in this select group. Cirrhotics lose a significant amount of skeletal muscle mass with disease progression [30], and critical illness only worsens the already present sarcopenia in these patients. Interestingly, only 8% of the

DOI: http://dx.doi.org/10.18053/jctres.08.202203.006

patients were malnourished according to the BMI (<18.5 kg/m$^2$) criteria. Although, there was a significant difference between the BMI of patients with and without sarcopenia, not all the patients with sarcopenia could be classified as malnourished taking only BMI into consideration. The majority of sarcopenic patients have a BMI that falls in the normal category. Hence, physical appearance can be misleading while diagnosing sarcopenia, especially among cirrhotics due to altered hydration status. Our results also demonstrated that patients with sarcopenia had a significantly lower SMD as compared to those without sarcopenia, suggesting that not only the quantity but the quality of the muscles is also compromised.

On assessing the effect of sarcopenia on survival, we found that 62.2% of the patients died in the ICU, with maximum mortality at 7 days. Further, we observed that sarcopenics had significantly higher mortality in the ICU. Nevertheless, we did not observe any significant difference in time to death between sarcopenics and non-sarcopenics. Sarcopenia *per se* increases the risk of mortality by almost 4 times. Sarcopenia was also identified as an independent predictor of in-hospital mortality in patients admitted to the LICU (OR=3.5 [1.32–9.33]; *P*=0.011). Likewise, in a retrospective study of general critically ill patients, sarcopenia, as assessed by psoas muscle area, was identified as the independent predictor of in-ICU mortality [11]. Moreover, a meta-analysis investigating 14 studies and 3000 patients in all, also identified CT-defined sarcopenia as a predictor of mortality among critically ill patients [31].

In our study, the presence of sarcopenia was associated with a higher prevalence of sepsis in CICs, with sarcopenics having more sepsis-related mortality in the ICU. Likewise, in yet another study from our center, the incidence of post-liver transplant sepsis was found to be higher in sarcopenics and sepsis was identified as a perfect predictor of 90-day mortality in post-liver transplant patients [32]. Another study in liver transplant candidates reported a higher sepsis-related death among sarcopenics as compared to non-sarcopenics [26]. Higher post-liver transplant infections have also been reported in sarcopenics. However, in our study, the incidence of NOI was comparable between sarcopenics and non-sarcopenics. Plausibly a reduced muscle mass impairs immunity and physiological functions, making sepsis as one of the leading causes of death in sarcopenic patients with cirrhosis [33].

We also found a trend toward a higher incidence of feed intolerance among patients with sarcopenia. The reasons for feed intolerance are not clear but could be due to a high prevalence of shock, abdominal Koch's, and SBP in this particular group of patients. Since ours is the first prospective follow-up study in CICs, any comparisons with other studies on this aspect are not easy.

One retrospective study in critically ill patients with cirrhosis found a strong correlation between rapid muscle loss (of >2% per year) before ICU admission and mortality [12]. For the 1$^{st}$ time, in our study, we have demonstrated the impact of sarcopenia on the clinical outcomes prospectively among CICs. It is duly noted that sarcopenia influences the outcomes in chronic diseases [34] and it becomes irreversible once the patient reaches the ICU. Cirrhosis is a state of accelerated starvation, which leads to a reduction in the glycogen stores, thus enhancing gluconeogenesis from muscle protein breakdown, thereby precipitating sarcopenia [35,36]. Sarcopenia in cirrhosis is secondary to the disease *per se* apart from the primary age-related phenomenon. Hence, early identification of sarcopenia along with appropriate nutritional therapy is the need of the hour in these patients with cirrhosis to combat sarcopenia and improve the outcomes in the ICU.

## 5. Conclusion

The prevalence of sarcopenia is high among CICs at the time of ICU admission, which not only predisposes them to a high risk of sepsis but also affects their survival in the ICU. The presence of sarcopenia itself should alert clinicians to the same extent as any other complication in cirrhosis, thus warranting timely identification and management.

## Acknowledgments

The authors are grateful to Dr. Y. K. Joshi, Sr. Professor, Department of Clinical Nutrition, Institute of Liver and Biliary Sciences, New Delhi, for his continuous intellectual input in conducting this study.

## Conflict of Interest

The authors declare no conflicts of interest.

## References

[1] Nadim MK, Durand F, Kellum JA, Levitsky J, O'Leary JG, Karvellas CJ, *et al.* Management of the Critically Ill Patient with Cirrhosis: A Multidisciplinary Perspective. J Hepatol 2016;64:717-35.

[2] Dasarathy S. Cause and Management of Muscle Wasting in Chronic Liver Disease. Curr Opin Gastroenterol 2016;32:159-65.

[3] Topan MM, Sporea I, Dănilă M, Popescu A, Ghiuchici AM, Lupusoru R, *et al.* Impact of Sarcopenia on Survival and Clinical Outcomes in Patients With Liver Cirrhosis. Front Nutr 2021;8:766451.

[4] Ando Y, Ishigami M, Ito T, Ishizu Y, Kuzuya T, Honda T, *et al.* Sarcopenia Impairs Health-related Quality of Life in Cirrhotic Patients. Eur J Gastroenterol Hepatol 2019;31:1550-6.

[5] Welch N, Attaway A, Bellar A, Alkhafaji H, Vural A, Dasarathy S. Compound Sarcopenia in Hospitalized Patients with Cirrhosis Worsens Outcomes with Increasing Age. Nutrients 2021;13:659.

[6] Kalafateli M, Mantzoukis K, Yau YC, Mohammad AO, Arora S, Rodrigues S, *et al*. Malnutrition and Sarcopenia Predict Post-liver Transplantation Outcomes Independently of the Model for End-stage Liver Disease Score. J Cachexia Sarcopenia Muscle 2017;8:113-21.

[7] Figueiredo F, Perez R, Freitas M, Kondo M. Comparison of Three Methods of Nutritional Assessment in Liver

Cirrhosis: Subjective Global Assessment, Traditional Nutritional Parameters, and Body Composition Analysis. J Gastroenterol 2006;41:476-82.

[8] Lee SJ, Janssen I, Heymsfield SB, Ross R. Relation between Whole-body and Regional Measures of Human Skeletal Muscle. Am J Clin Nutr 2004;80:1215-21.

[9] Moisey LL, Mourtzakis M, Cotton BA, Premji T, Heyland DK, Wade CE, *et al*. Nutrition and Rehabilitation Investigators Consortium (NUTRIC). Skeletal Muscle Predicts Ventilator-free Days, ICU-free Days, and Mortality in Elderly ICU Patients. Crit Care 2013;17:R206.

[10] Kou HW, Yeh CH, Tsai HI, Hsu CC, Hsieh YC, Chen WT, *et al.* Sarcopenia is an Effective Predictor of Difficult-to-wean and Mortality among Critically Ill Surgical Patients. PLoS One 2019;14:e0220699.

[11] Toptas M, Yalcin M, Akkoc İ, Demir E, Metin C, Savas Y, *et al.* The Relation between Sarcopenia and Mortality in Patients at Intensive Care Unit. Biomed Res Int 2018;2018:5263208.

[12] Ju S, Choi SM, Park YS, Lee CH, Lee SM, Yoo CG, *et al.* Rapid Muscle Loss Negatively Impacts Survival in Critically Ill Patients With Cirrhosis. J Intensive Care Med 2020;35:663-71.

[13] Fleming KM, Aithal GP, Solaymani-Dodaran M, Card TR, West J. Incidence and Prevalence of Cirrhosis in the United Kingdom, 1992-2001: A General Population-based Study. J Hepatol 2008;49:732-8.

[14] Sarin SK, Kedarisetty CK, Abbas Z, Amarapurkar D, Bihari C, Chan AC, *et al.* Acute-on-chronic Liver Failure: Consensus Recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. Hepatol Int 2014;8:453-71.

[15] Kvist H, Sjostrom L, Tylen U. Adipose Tissue Volume Determinations in Women by Computed Tomography: Technical Considerations. Int J Obes 1986;10:53-67.

[16] Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, *et al.* Fitness, Life Enhancement, and Exercise in Liver Transplantation Consortium. A Multicenter Study to Define Sarcopenia in Patients with End-stage Liver Disease. Liver Transpl 2017;23:625-33.

[17] Torriani M, Hadigan C, Jensen ME, Grinspoon S. Psoas Muscle Attenuation Measurement with Computed Tomography Indicates Intramuscular Fat Accumulation in Patients with the HIV-lipodystrophy Syndrome. J Appl Physiol (1985) 2003;95:1005-10.

[18] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43:304-77.

[19] van Vught LA, Klein Klouwenberg PM, Spitoni C, Scicluna BP, Wiewel MA, Horn J, *et al.* MARS Consortium. Incidence, Risk Factors, and Attributable Mortality of Secondary Infections in the Intensive Care Unit after Admission for Sepsis. JAMA 2016;315:1469-79.

[20] Acute Kidney Injury Work Group. Kidney Disease: Improving Global Outcome (KDIGO)-Clinical practical Guidelines for Acute Kidney Injury. Kidney Inter 2012;2:1-138.

[21] Nayak SL, Maiwall R, Nandwani A, Ramanarayanan S, Mathur RP, Kumar R, *et al.* Management of Acute Kidney Injury in Cirrhosis. Hepatol Int 2013;7:813-9.

[22] Nguyen NQ, Fraser RJ, Chapman MJ, Bryant LK, Holloway RH, Vozzo R, *et al.* Feed Intolerance in Critical Illness is Associated with Increased Basal and Nutrient-stimulated Plasma Cholecystokinin Concentrations. Crit Care Med 2007;35:82-8.

[23] Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver Validation of Skeletal Muscle Measurement by Magnetic Resonance Imaging and Computerized Tomography. J Appl Physiol (1985) 1998;85:115-22.

[24] Weijs PJ, Looijaard WG, Dekker IM, Stapel SN, Girbes AR, Oudemans-van Straaten HM, *et al.* Low Skeletal Muscle Area is a Risk Factor for Mortality in Mechanically Ventilated Critically Ill Patients. Crit Care 2014;18:R12.

[25] Cox MC, Booth M, Ghita G, Wang Z, Gardner A, Hawkins RB, *et al.* The Impact of Sarcopenia and Acute Muscle Mass Loss on Long-term Outcomes in Critically Ill Patients with Intra-abdominal Sepsis. J Cachexia Sarcopenia Muscle 2021;12:1203-13.

[26] Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, *et al.* Muscle Wasting is Associated with Mortality in Patients with Cirrhosis. Clin Gastroenterol Hepatol 2012;10:166-73.

[27] Kang SH, Jeong WK, Baik SK, Cha SH, Kim MY. Impact of Sarcopenia on Prognostic Value of Cirrhosis: Going Beyond the Hepatic Venous Pressure Gradient and MELD Score. J Cachexia Sarcopenia Muscle 2018;9:860-70.

[28] Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CM, Sawyer MB, Beaumont C, *et al*. Sarcopenic Obesity and Myosteatosis are Associated with Higher Mortality in Patients with Cirrhosis. J Cachexia Sarcopenia Muscle 2016;7:126-35.

[29] Lucidi C, Lattanzi B, Di Gregorio V, Incicco S, D'Ambrosio D, Venditti M, *et al.* A Low Muscle Mass Increases Mortality in Compensated Cirrhotic Patients with Sepsis. Liver Int 2018;38:851-7.

[30] Kalafateli M, Konstantakis C, Thomopoulos K, Triantos C. Impact of Muscle Wasting on Survival in Patients with Liver Cirrhosis. World J Gastroenterol 2015;21:7357-61.

[31] Zhang XM, Chen D, Xie XH, Zhang JE, Zeng Y, Cheng AS. Sarcopenia as a Predictor of Mortality among the Critically Ill in an Intensive Care Unit: A Systematic Review and Meta-analysis. BMC Geriatr 2021;2:339.

[32] Kumar V, Benjamin J, Shasthry V, Bharathy KG, Sinha PK,

Kumar G, *et al.* Sarcopenia in Cirrhosis: Fallout on Liver Transplantation. J Clin Exp Hepatol 2020;10:467-76.

[33] Wong CH, Weiss D, Sourial N, Karunananthan S, Quail JM, Wolfson C, *et al.* Frailty and its Association with Disability and Comorbidity in a Community-dwelling Sample of Seniors in Montreal: A Cross-sectional Study. Aging Clin Exp Res 2010;22:54-62.

[34] Meyer F, Valentini L. Disease-related Malnutrition and Sarcopenia as Determinants of Clinical Outcome. Visc Med 2019;35:282-91.

[35] Gass C, Hipskind P, Tsien C, Malin SK, Kasumov T, Shah SN, *et al.* Sarcopenia and a Physiologically Low Respiratory Quotient in Patients with Cirrhosis: a Prospective Controlled Study. J Appl Physiol 2013;114:559-65.

[36] Peng S, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body Composition, Muscle Function, and Energy Expenditure in Patients with Liver Cirrhosis: A Comprehensive Study. Am J Clin Nutr 2007;85:1257-66.



DOI: http://dx.doi.org/10.18053/jctres.08.202203.006