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Enhancing ACLF prediction by integrating sarcopenia assessment and frailty in liver transplant candidates on the waiting list

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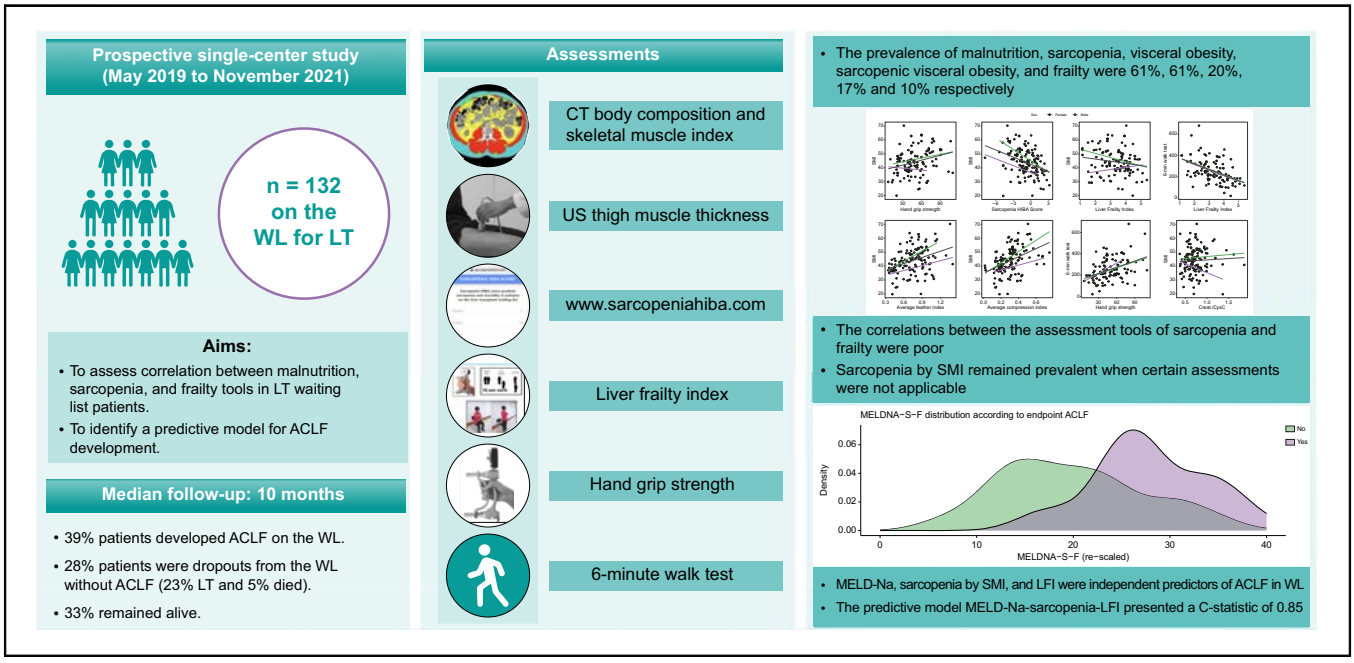
Graphical abstract



Highlights

- The correlations between the assessment tools for sarcopenia and frailty were poor.
- MELD-Na, sarcopenia by SMI, and LFI were independent predictors of ACLF in patients on the WL.
- The predictive model MELD-Na-sarcopenia-LFI achieved a C-statistic for the prediction of ACLF of 0.85.
- The CLIF-C ACLF score correlated with WL mortality, whereas baseline parameters for physiological functional reserve did not.

Impact and implications

The relationship between sarcopenia and frailty assessment tools, as well as their ability to predict acute-on-chronic liver failure (ACLF) in patients on the liver transplant (LT) waiting list (WL), remains poorly understood. Existing objective frailty screening tests have limitations when applied to critically ill patients. The correlation between sarcopenia and frailty assessment tools was weak, suggesting that they may capture different phenotypes. Sarcopenia assessed by skeletal muscle index, frailty evaluated using the liver frailty index, and the model for end-stage liver disease-Na score independently predicted the development of ACLF in patients on the WL. Our findings support the integration of liver frailty index and skeletal muscle index assessments at the time of inclusion on the WL for LT. This combined approach allows for the identification of a specific patient subgroup with an increased susceptibility to ACLF, underscoring the importance of early implementation of targeted treatment strategies to improve outcomes for patients awaiting LT.

Research article

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Enhancing ACLF prediction by integrating sarcopenia assessment and frailty in liver transplant candidates on the waiting list

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Background & Aims: Malnutrition, sarcopenia, and frailty are prevalent in cirrhosis. We aimed to assess the correlation between assessment tools for malnutrition, sarcopenia, and frailty in patients on the liver transplant (LT) waiting list (WL), and to identify a predictive model for acute-on-chronic liver failure (ACLF) development.
Methods: This prospective single-center study enrolled consecutive patients with cirrhosis on the WL for LT (May 2019-November 2021). Assessments included subjective global assessment, CT body composition, skeletal muscle index (SMI), ultrasound thigh muscle thickness, sarcopenia HIBA score, liver frailty index (LFI), hand grip strength, and 6-minute walk test at enrollment. Correlations were analyzed using Pearson's correlation. Competing risk regression analysis was used to assess the predictive ability of the liver- and functional physiological reserve-related variables for ACLF.
Results: A total of 132 patients, predominantly with decompensated cirrhosis (87%), were included. Our study revealed a high prevalence of malnutrition (61%), sarcopenia (61%), visceral obesity (20%), sarcopenic visceral obesity (17%), and frailty (10%) among participants. Correlations between the assessment tools for sarcopenia and frailty were poor. Sarcopenia by SMI remained prevalent when frailty assessments were not usable. After a median follow-up of 10 months, 39% of the patients developed ACLF on WL, while 28% experienced dropouts without ACLF. Multivariate analysis identified MELD-Na, SMI, and LFI as independent predictors of ACLF on the WL. The predictive model MELD-Na-sarcopenia-LFI had a C-statistic of 0.85.
Conclusions: The poor correlation between sarcopenia assessment tools and frailty underscores the importance of a comprehensive evaluation. The SMI, LFI, and MELD-Na independently predicted ACLF development in WL. These findings enhance our understanding of the relationship between sarcopenia, frailty, and ACLF in patients awaiting LT, emphasizing the need for early detection and intervention to improve WL outcomes.
Impact and implications: The relationship between sarcopenia and frailty assessment tools, as well as their ability to predict acute-on-chronic liver failure (ACLF) in patients on the liver transplant (LT) waiting list (WL), remains poorly understood. Existing objective frailty screening tests have limitations when applied to critically ill patients. The correlation between sarcopenia and frailty assessment tools was weak, suggesting that they may capture different phenotypes. Sarcopenia assessed by skeletal muscle index, frailty evaluated using the liver frailty index, and the model for end-stage liver disease-Na score independently predicted the development of ACLF in patients on the WL. Our findings support the integration of liver frailty index and skeletal muscle index assessments at the time of inclusion on the WL for LT. This combined approach allows for the identification of a specific patient subgroup with an increased susceptibility to ACLF, underscoring the importance of early implementation of targeted treatment strategies to improve outcomes for patients awaiting LT.

Introduction

In recent years, functional physiological reserves have become very important in the field of cirrhosis.[1] Patients with cirrhosis exhibit accelerated aging associated with a decrease in physiological reserve, resulting in greater vulnerability and decreased responsiveness to injury or pathological processes.[2]

Keywords: Sarcopenia; Frailty; ACLF; Liver Transplant.
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Malnutrition, sarcopenia, and physical frailty are the three entities characterized by low physiological functional reserves that are most commonly studied in patients with cirrhosis.[3] Recent guidelines have defined and provided assessment tools for cirrhosis, emphasizing the importance of early detection and treatment.[3,4] Malnutrition is characterized by an imbalance (deficiency or excess) of nutrients that has measurable adverse effects on tissue/body form (body shape, size, and composition), function, and/or clinical outcome.[1] The subjective global assessment (SGA) has been shown to independently predict liver transplant (LT)-free survival and clinical deterioration.[5] However it correlates poorly with other measures and tends to underestimate muscle loss in patients with cirrhosis.[6] Sarcopenia is defined as a phenotypic representation of loss of muscle mass, with the skeletal muscle index (SMI) using CT or MRI as the gold standard for diagnosis.[1,3] In addition, CT allows for determination of body composition and estimation of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).[7] However, the cost and radiation risk limit the use of this method for screening and follow-up of sarcopenia.[1] In this context, different tools, such as thigh muscle thickness measured by ultrasound (US),[8] or clinical-serological scores based on the creatinine/cystatin C ratio, such as the sarcopenia HIBA score,[9] have emerged as surrogate tools for detecting these conditions. Finally, frailty in patients with cirrhosis is the phenotypic representation of impaired contractile muscle function,[3,4] with the liver frailty index (LFI),[10] 6-minute walk test (6MWT),[11] and handgrip strength (HGS)[12] being the three most valid objective tools in advanced liver disease.

These conditions have been thoroughly studied in patients on the waiting list (WL) for LT.[13] All three are associated with increased WL mortality beyond the model for end-stage liver disease (MELD) score alone,[14] as they are predictors of risk of hospitalization, disability, and progression to cirrhosis, as well as determinants of higher morbidity and mortality after LT.[3,4,15,16] In the setting of WL, the primary cause of death is multiorgan failure from a decompensating event that leads to acute-on-chronic liver failure (ACLF).[16,17]

Nonetheless, there is scarce evidence regarding the suitability of sarcopenia and frailty assessment tools, particularly in patients with further decompensation, and their correlation and predictive significance in ACLF development.

Our aim was to assess the correlation between the main assessment tools for malnutrition (SGA and body composition by CT), sarcopenia (SMI, thigh muscle thickness measured by US, and sarcopenia HIBA score), and frailty (LFI, HGS, and 6MWT) in patients enrolled on the WL, and to find the best predictive model based on these tools for the development of ACLF in patients on the WL for LT.

Patients and methods

Patients

This single-center, prospective, observational study included all consecutive patients with cirrhosis at the time of enrollment on the WL for LT (May 2019 to November 2021) at the Hospital Italiano de Buenos Aires (HIBA). The assessment protocol prior to LT included a 3-day hospitalization period for the patients to perform the diagnostic tests. The patients were evaluated by a multidisciplinary team. From their admission to WL for LT, patients were followed by the LT team and completed the following controls according to the model for end-stage liver disease-sodium (MELD-Na) score or the clinical criteria of the treating physician. All variables, including the presence of SGA, body composition by CT, thigh muscle thickness measured by US, sarcopenia HIBA score, LFI, HGS, and 6MWT were collected at the time of inclusion on the WL.

Regarding ACLF, patients were followed from inclusion on the WL until the development of ACLF, death/waitlist dropout, LT, or the last date of follow-up. Patients with hepatocellular carcinoma (HCC) outside the Milan criteria, patients without clinical or histological evidence of cirrhosis, patients with active extrahepatic neoplasms, patients with concurrent simultaneous liver-kidney transplant, and those who were listed for liver retransplantation were excluded.

Baseline assessments at WL inclusion

Data related to comorbidities (BMI, arterial hypertension, and diabetes) and liver disease (etiology, LT indication, history of decompensation, and laboratory tests) were collected at the time of listing for LT. In addition, renal function was evaluated by different methods: serum levels of CysC (Human Cystatin C Kit – SPAplus® - Binding Site Group, Birmingham, UK) and estimated glomerular filtration rate (eGFR) by MDRD-6 (modification of diet in renal disease-6).[18] The MELD,[19] MELD-Na,[20] MELD 3.0,[21] MELD-CysC[22] GEMA-Na[23] and MELD-sarcopenia[24] scores were calculated at inclusion in the WL for LT. Finally, at the time of inclusion on the WL, nutritional assessment was performed by SGA;[25] body composition was assessed by CT at the third lumbar vertebrae (L3) level;[7] sarcopenia was assessed by CT SMI at the L3 level, [26] sarcopenia HIBA score,[9] and thigh muscle thickness measured by US;[8] frailty was assessed by LFI,[10] HGS,[12] and 6MWT.[11]

Study definitions

- SGA: SGA divides patients into three categories based on five history parameters (*i.e.*, weight change, dietary intake relative to usual, gastrointestinal symptoms, functional capacity, and metabolic stress of underlying diagnosis) and three physical examination parameters (loss of subcutaneous fat, loss of muscle mass, and edema/ascites). The three SGA categories are: A, well nourished; B, moderately malnourished; and C, severely malnourished.[5]
- Sarcopenia by SMI: We used CT or MRI at the L3 level, performed within the LT evaluation, and analyzed with Alma Medical Imaging 4.2.0.25 (ALMA IT Systems® 2005-2014) and Coreslicer® 1.0. The skeletal muscle was identified and quantified, and the cross-sectional area of the muscle was normalized to height (cm^2/m^2), as reported in previous studies. The muscles in the L3 region include the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and the rectus abdominis. All CT scans were analyzed by junior radiologists (JS) and two senior radiologists (LS and JCS), who were blinded to the outcome. SMI was expressed as the cross-sectional L3 muscle area/height.[2] Sarcopenia was defined by previously established cut-off points of SMI <50 cm^2/m^2 for men and <39 cm^2/m^2 for women, which have proven to be associated with pre-transplant mortality independent of age and MELD score.[26]
- Body composition: Body composition was assessed using secondary analysis of abdominal CT scans as part of the LT evaluation. CT-based measures of VAT and SAT were quantified (cm^2) at the L3 level using Coreslicer® software, which enabled specific tissue demarcation using standard

Hounsfield Unit thresholds of −29 to 150 for skeletal muscle, −150 to −50 for VAT, and −190 to −30 for SAT. As reported in previous studies using these specific Hounsfield Unit thresholds, tissue areas are outlined on an individual CT section/slice by a junior (JS) and 2 senior (LS and JCS) radiologists resulting in a semiautomatic computed total cross-sectional area (cm^2) by summing tissue pixels and multiplying by pixel surface area.[27] All values were normalized by height (m^2), resulting in VAT index (cm^2/m^2), and SAT index (cm^2/m^2). The VSR (visceral-to-subcutaneous adipose tissue ratio) was calculated by dividing the VAT index by the SAT index.[30] We then defined visceral obesity (VSR ≥1.54 for men and ≥1.37 for women) and sarcopenic visceral obesity as the combination of sarcopenia by SMI and visceral obesity, as reported in previous studies.[27]

- Thigh muscle thickness measured by US: The right thigh muscle thickness was measured using bedside US by a senior (SB) radiologist, who was blinded to all clinical data. Based on published experience, points at one-third and one-half of the total distance from the top of the patella to the iliac crest were marked, respectively. One reading was obtained at each point: a compression reading taken by pressing the probe downward until no further compression of the muscles was possible and a featherweight reading where the probe was held without pressure on the thigh. Measurements at both points were averaged and corrected for stature (height^2) to yield an average compression index and an average feather index.[8]
- Sarcopenia HIBA score: Based on the previous study, it was calculated with the variables sex, BMI, Child-Pugh, and creatinine/CysC ratio based on the equation available at www.sarcoepniahiba.com.[9]
- 6MWT: The distance walked in meters for 6 min at the usual speed was evaluated.[11]
- HGS: The average of three trials, measured in the patient's dominant hand using a hand dynamometer (Jamar®) in the standard position, was evaluated.[12]
- LFI: Three performance-based tests: HGS, time to perform five chair stands, time holding three balance positions, as reported in previous studies. The LFI was calculated based on the equation available at https://liverfrailtyindex.ucsf.edu/, and three categories were defined: robust (<3.2), pre-frail (3.2-4.5) and frail (>4.5).[10]
- ACLF: ACLF was defined and graded according to the EASL-CLIF criteria in patients with cirrhosis who required hospitalization and had acute decompensation. Specific organ failures were determined according to the CLIF consortium organ failures score.[28]

Outcomes

- *ACLF on the WL:* For this outcome, patients were followed from inclusion on the WL to the development of ACLF, death/waitlist dropout (not by ACLF), LT, or the last date of follow-up. The triggering event, laboratory test, number and type of organ failures, grade of ACLF, CLIF-C ACLF[29] score, MELD, MELD-Na, MELD 3.0, and MELD-sarcopenia, at the diagnosis of ACLF were evaluated.
- *Mortality on the WL:* Mortality while on the WL was evaluated. For this outcome, the patients were followed up until death, LT, or the date of the last follow-up.
- Finally, post-LT survival was monitored until the last day of follow-up (12.26.22), and the causes of death were recorded.

Ethical considerations

The study was performed in accordance with the Declaration of Helsinki and the E6 Good Clinical Practice Standards ICH, as well as the Guide for Human Health Research (Resolution 1480/11) of the Ministry of Health of the Nation. All personal data were codified in accordance with the Organic Law 25,325 of 30 October 2000 on the Protection of Personal Data in Argentina. All the study data was treated anonymously with restricted access by only authorized personnel for the purposes of the study. This study was approved by the Institutional Review Board of the Hospital Italiano Buenos Aires (protocol number 5412).

Statistical analysis

Median (IQR) was used to describe quantitative variables and n (%) was used for qualitative variables. Differences between qualitative variables were compared using the chi-square test or Fisher's exact test, when indicated. Quantitative variables were analyzed using non-parametric tests (Mann-Whitney or Kruskal-Wallis for unpaired samples). Pearson's correlation analysis was performed considering the overall relationship between the variables and the sex of the patients.

Fine and Gray competing risk regression analysis (with LT and death as the competing risks for ACLF on the WL) and multivariable Cox regression analysis of cause-specific hazards were performed to evaluate variables associated with ACLF on the WL. The strength of associations is presented as subdistribution hazard ratios (sHRs) and cause-specific hazard ratios (HRs) with 95% CIs. A multivariable model was fitted that was simplified by means of a backward selection process of nested models using the Bayesian information criterion as the selection criterion. This index (lower value: better model) takes the logarithm of the likelihood and penalizes it based on the number of model parameters to avoid overfitting. After performing an analysis using a multivariable Cox regression model, a new score was constructed using the resulting simplified model. Internal validation analysis was performed by bootstrapping, which has been shown to be a more efficient procedure than splitting the sample.[30]

To make the new score derived from the regression formula more intelligible we re-scaled it with the following formula: y= [(x-xmin)/xrange]n; where Y is the adjusted variable, X is the original variable, Xmin is the minimum observed value of the original variable, Xrange is the difference between the maximum potential score and the minimum potential score on the original variable, and n is the upper limit of the rescaled variable. The score was rounded to the next integer. Model discrimination (Harrell's C-statistic) was tested for the endpoint of ACLF. A comparison of the discrimination between the new model and MELD-Na was conducted using a U-statistic, based on all possible pairs of observations, and counting the fraction of pairs for which one model was more concordant with the outcome than the other model. In this context, the informative pairs of patients are those wherein one of the individuals develops the event and the other does not (provided the one not having the event is not censored earlier than the one having the event), and those in which both individuals develop the event at different times during follow-up. We used for this purpose the function rcorrp.cens from the *Hmisc* package (Harrell Jr F (2022). Hmisc: Harrell Miscellaneous. R package version 4.2.2).

All tests were two-tailed and a p value less than 0.05 was considered statistically significant. R (version 4.2.2) and SPSS (v.29.0) were used for statistical analyses.

Results

Patients

One-hundred-thirty-two patients were included. The indications for LT were decompensated cirrhosis (87%) and compensated cirrhosis with HCC (13%), and the prevalence of HCC was 23%. The main patient characteristics are summarized in Table 1. SGA, sarcopenia by SMI, thigh muscle thickness by US, and sarcopenia HIBA score were evaluated in all included patients, whereas LFI and HGS were evaluated in 115/132 (87%) and 6MWT in 105/132 (80%) patients, depending on the patient's ability to perform the diagnostic tests. Similarly, body composition was evaluated in 100/132 (76%) patients depending on the availability of CT scans at the time of the pre-LT evaluation. The median time between inclusion on the WL and radiological evaluation was 1 (0-2) days. The median BMI was 27 (24-32), with a prevalence of obesity of 39%, while in patients where body composition was evaluated, the prevalence of visceral obesity was 20%. The prevalence of malnutrition (SGA B/C), sarcopenia, sarcopenic visceral obesity and frailty was 61%, 61%, 17%, and 10%, respectively.

Table 1. Characteristics of the cohort

Characteristics at inclusion on the waiting list	n (%)/median (IQR)
Age (years)	60 (47-64)
Sex, female	43 (32.6)
BMI (kg/m^2)	27 (24-32)
Etiology	
HCV	10 (7.6)
HBV	2 (1.5)
Alcohol	53 (40.2)
NASH	26 (19.7)
Primary biliary cholangitis	11 (8.3)
Primary sclerosing cholangitis	6 (4.5)
Autoimmune hepatitis	15 (11.4)
Cryptogenic	9 (6.9)
Liver transplant indication, compensated cirrhosis with HCC	17 (12.9)
HCC presence	31 (23.5)
Diabetes	42 (31.8)
Arterial hypertension	65 (49.2)
History of ascites	96 (72.7)
Refractory ascites	8 (6.1)
History of encephalopathy	58 (43.9)
History of variceal bleeding	37 (28)
Primary prophylaxis of CSPH	45 (34.1)
History of spontaneous infections	26 (19.7)
Primary SBP prophylaxis	12 (9.1)
Leukocytes (10^9/L)	4.36 (3.05-5.78)
Platelets (10^9/L)	92 (61-139.9)
AST (IU/L)	39 (26-56)
ALT (IU/L)	28 (18-48)
Bilirubin (mg/dl)	1.81 (1.09-4.21)
INR	1.53 (1.33-1.96)
Albumin (g/dl)	3.01 (2.54-3.41)
Urea (mg/dl)	32 (24-45)
Na (mmol/L)	136 (132-138)
Creatinine (mg/dl)	0.81 (0.62-1.09)
CysC (mg/L)	1.21 (0.92-1.56)
eGFR (ml/min/1.73 m^2)	86 (59-119)
Child-Pugh class	
A	32 (24.2)
B	53 (40.2)
C	47 (35.6)
MELD-Na	18 (11-23)
MELD-CysC	13 (8-17)
MELD 3.0	19 (12-24)
GEMMA NA	18 (13-24)
MELD sarcopenia	23 (15-29)
Subjective global assessment	
A	51 (38.6)
B	51 (38.6)
C	30 (22.7)
Visceral adipose tissue index (cm^2/m^2) (n = 100)	45.38 (30.53-67.84)
Subcutaneous adipose tissue index (cm^2/m^2) (n = 100)	60.89 (42.24-89.89)
Viseral subcutaneous ratio (n = 100)	0.74 (0.45-1.37)
Visceral obesity (n = 100)	20 (20)
Skeletal muscle index (cm^2/m^2) (SMI)	43.92 (37.89-50.10)
Sarcopenia by SMI	80 (60.6)
Sarcopenic visceral obesity (n = 100)	17 (17)
Average feather index (cm^2/m^2)	0.73 (0.58-0.89)
Average compression index (cm^2/m^2)	0.30 (0.20-0.37)
Sarcopenia HIBA score	-0.72 (-2 to 0.62)
6-min walk test (meters) (n = 105)	234 (186-322)
6-min walk test <250 m	57 (54)
Hand grip strength (average) (n = 115)	44 (33.33-63.33)
Liver frailty index (numeric) (n = 115)	3.50 (2.70-4.03)
Liver frailty index score (categorized) (n = 115)	
Robust	51 (44.3)
Pre-frail	52 (45.2)
Frail	12 (10.4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; HIBA, Hospital Italiano de Buenos Aires; INR, international normalized ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; SBP, spontaneous bacterial peritonitis; SMI, skeletal muscle index.

Association between sarcopenia and frailty in patients with cirrhosis on the WL for LT

Of the 115 patients who were jointly assessed for the presence of SMI sarcopenia and LFI frailty, 67/115 (58%) had sarcopenia and 12/115 (10%) had frailty. Similarly, in 86 patients, the disposition of fat, sarcopenia, and frailty was evaluated together, with a prevalence of sarcopenic visceral obesity of 15% (13/86). Fig. 1 shows the percentage of patients with sarcopenia by SMI and sarcopenic visceral obesity, depending on whether the patient was robust, pre-frail, or frail. The correlations between the different sarcopenia assessment tools and objective frailty assessment tools are shown in Table 2 and Fig. 2. Although in male the correlations between the different tools were significant, the degree of correlation, except for the SMI-sarcopenia HIBA score and SMI-average compression index, was poor. Likewise, in females, the SMI-sarcopenia HIBA score, LFI-6MWT, and HGS-6MWT presented a significant but low correlation. As expected, among 12/13 (92.3%) patients unable to undergo LFI and 16/19 (84.2%) unable to undergo 6MWT, sarcopenia was diagnosed based on SMI.

ACLF development in patients on the WL

After a median follow-up of 10 (3-21) months, 51/132 (39%) patients developed ACLF on the WL, 37/132 (28%) patients were drop-outs from the WL without ACLF (30 underwent LT, and 7 died: 2 due to cardiovascular events, 4 due to progression of HCC, and 1 due to development of colorectal cancer), and 44/132 (33%) remained alive and still on the WL for LT. The median time between WL inclusion and ACLF was 4 months. The percentages

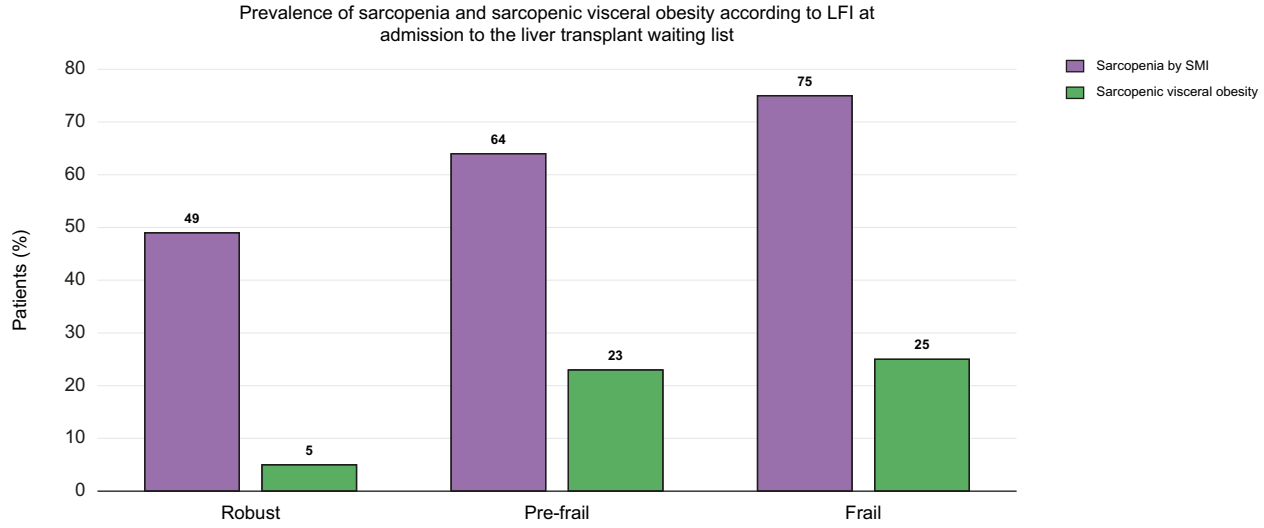

Fig. 1. Prevalence of sarcopenia and sarcopenic visceral obesity according to LFI at admission to the liver transplant waiting list. LFI, liver frailty index; SMI, skeletal muscle index.

of patients with ACLF grades I, II, and III were 59%, 22%, and 20%, respectively. The main patient characteristics at the time of ACLF are shown in Table S1. The main characteristics associated with the development of ACLF were history of ascites, presence of further decompensation of cirrhosis, and high Child-Pugh and MELD-Na scores. Finally, all instruments assessing physiological functional reserve (SGA, sarcopenia by SMI, average feather index by US, sarcopenia HIBA score, LFI, HGS, and 6MWT) were associated with the development of ACLF in the univariable analysis (Table 3). In the multivariable analysis, after adjusting for MELD-Na, SGA, sarcopenia by SMI, sarcopenia HIBA score, average feather index, LFI, and HGS (Table S2), elevated values of MELD-Na at WL inclusion were independent predictors of ACLF development on the WL (sHR 1.08, 95% CI 1.03-1.14, $p = 0.003$). In addition, within the instruments assessing sarcopenia and frailty, sarcopenia by SMI (sHR 3.05, 95% CI 1.28-7.27, $p = 0.012$) and LFI (continuous values, sHR 1.54, 95% CI % 1.02-2.32, $p = 0.042$) were independent predictors of ACLF on the WL.

Table 2. Correlation between the different assessment tools for sarcopenia and frailty.

x	y	Pearson's correlation coefficient	*p* value
Whole cohort			
Hand grip strength	SMI	0.27	**0.003**
Sarcopenia HIBA score	SMI	-0.36	**<0.001**
Average feather index	SMI	0.35	**<0.001**
Average compression index	SMI	0.43	**<0.001**
Liver frailty index	SMI	-0.16	0.090
Liver frailty index	6-min walk test	-0.46	**<0.001**
Hand grip strength	6-min walk test	0.40	**<0.001**
Ratio creatinine/cystatin C	SMI	0.05	0.584
Males			
Hand grip strength	SMI	0.22	**0.049**
Sarcopenia HIBA score	SMI	-0.60	**<0.001**
Average feather index	SMI	0.55	**<0.001**
Average compression index	SMI	0.61	**<0.001**
Liver frailty index	SMI	-0.31	**0.006**
Liver frailty index	6-min walk test	-0.42	**<0.001**
Hand grip strength	6-min walk test	0.38	**0.001**
Ratio creatinine/cystatin C	SMI	0.08	0.435
Females			
Hand grip strength	SMI	-0.08	0.646
Sarcopenia HIBA score	SMI	-0.31	**0.040**
Average feather index	SMI	0.31	**0.039**
Average compression index	SMI	0.28	0.067
Liver frailty index	SMI	0.19	0.258
Liver frailty index	6-min walk test	-0.55	**<0.001**
Hand grip strength	6-min walk test	0.49	**0.003**
Ratio creatinine/cystatin C	SMI	-0.25	0.101

Pearson's correlation analysis was performed considering the overall relationship between the variables and the sex of the patients. HIBA, Hospital Italiano de Buenos Aires; SMI, skeletal muscle index.

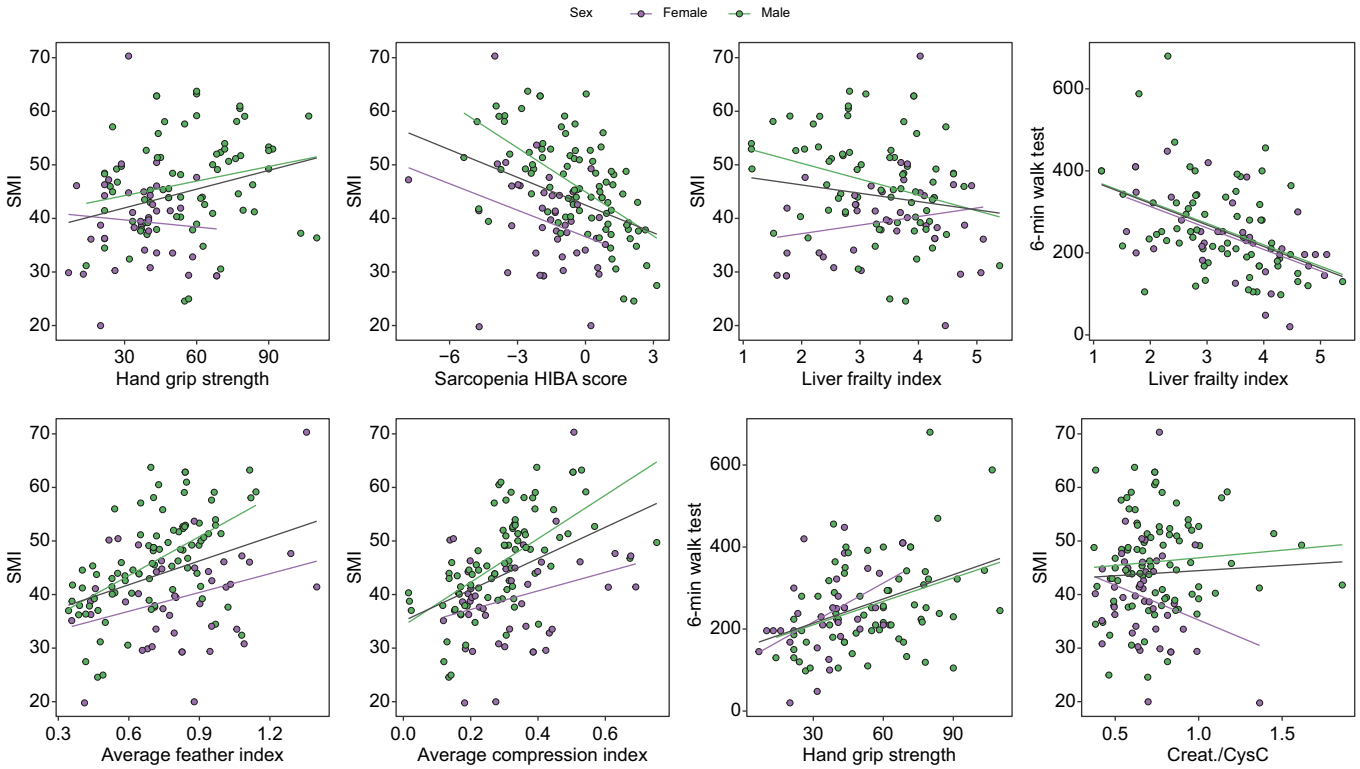

Fig. 2. Correlation between the different objective tools for assessing physiological functional reserve. Pearson's correlation analysis was performed considering the overall relationship between the variables and the sex of the patients. HIBA, Hospital Italiano de Buenos Aires; SMI, skeletal muscle index.

MELD-Na-sarcopenia-frailty score: the concepts of relative explained variation

To develop a tool that could discriminate between patients developing or not ACLF on the WL for LT, we used a Cox regression analysis. As with competing risk analysis, after performing Cox regression analysis, the MELD-Na (HR 1.17, 95% CI 1.09-1.24, p <0.001), presence of sarcopenia by SMI (HR 3.92, 95% CI 1.60-9.63, p = 0.003), and LFI (HR 1.97, 95% CI 1.31-2.95, p = 0.001), were independent predictors of the development of ACLF. The MELD-Na-sarcopenia-frailty score, re-scaled to range from 6-40 was defined according to the following formula: ((((MELD -Na * 0.154 + Sarcopenia * 1.36 + LFI * 0.675)-1.973)/7.431)*34)+6. The score is then rounded to the next integer. The bootstrapped corrected C-statistic for the development of ACLF was 0.85. The C-statistic for the MELD-Na score was 0.83. When comparing the discrimination of the two models, the MELD-Na-sarcopenia-LFI was more concordant with the risk of ACLF in 74% of the potential comparisons, while MELD-Na was better in 26% of the cases (p <0.001). Fig. 3 shows the comparison with MELD-Na and how MELD-Na-sarcopenia-LFI can improve discrimination between patients with and without ACLF.

Evolution of patients with ACLF on the WL and post-LT survival

Of the 51 patients who presented with ACLF while on the WL, after a median follow-up on the WL of 25 (11–200) days, 21 (41%) died with a median time between ACLF and death of 20 (11-148) days. Twenty-three (45%) patients underwent LT with a median time between ACLF and LT of 21 (5-43) days, and 7 (14%) remained alive until the last follow-up. The factors associated with mortality on the WL were higher leukocyte count (sHR 1.10, 95% CI 1.09-1.11, p = 0.029), presence of brain failure (sHR 3.66, 95% CI 1.48-9.04, p = 0.005), the presence of circulatory failure (sHR 3.53, 95% CI 1.46-8.50, p = 0.005), the presence of respiratory failure (sHR 38.68, 95% CI 11.36-131.65, p <0.001), and ACLF grade (sHR 2.96, 95% CI 1.69-5.19, p <0.001). The CLIF-C ACLF score captures the association of these factors with mortality on the WL (sHR 1.07, 95% CI 1.01-1.13, p = 0.018). None of the baseline parameters for evaluating physiological functional reserve were associated with mortality on the WL in the subgroup of patients with ACLF. Table 4 shows the main characteristics associated with mortality on the LT WL.

Of the 23 patients who underwent transplantation with ACLF, after a median follow-up of 19 (10-26) months, 8/23 (35%) died after the LT (2 due to COVID-19, 3 due to cardiovascular events, and 3 due to sepsis).

Discussion

The prevalence of malnutrition, sarcopenia, and frailty in patients on the WL for LT has been widely reported as a prognostic factor.[3] However, the applicability of the different assessment tools, the correlation between them, and the overlap between sarcopenia and frailty have been less studied.[4] In our prospective cohort, the prevalence of malnutrition was 61% (SGA B/C) and that of sarcopenia (by SMI) was 61%, while 17% had sarcopenic visceral obesity and 10% frailty by LFI. The applicability of the different assessment tools was very different between those that assessed muscle mass (sarcopenia, ~100%) and muscle functionality (frailty, ~84%), with disease severity having an impact

Table 3. Characteristics associated with the development of ACLF in WL for LT.

Characteristics at inclusion on the waiting list	Alive n (%)/median (IQR)	ACLF n (%)/median (IQR)	sHR (95% CI)	*p* value
Age (years)	49 (42-64)	62 (52-66)	1.01 (0.99-1.04)	0.330
Sex, female	19 (43.2)	14 (27.5)	1.12 (0.61-2.05)	0.720
BMI (kg/m^2)	27 (24-32)	28 (24-32)	0.99 (0.94-1.05)	0.840
Etiology				
HCV	0	5 (9.8)		
HBV	0	2 (3.9)		
Alcohol	15 (34.1)	23 (45.1)		
NASH	9 (20.5)	9 (17.6)		
Primary biliary cholangitis	4 (9.1)	4 (7.8)	0.91(0.81-1.03)	0.131
Primary sclerosing cholangitis	4 (9.1)	1 (2)		
Autoimmune hepatitis	7 (15.9)	5 (9.8)		
Cryptogenic	5 (11.4)	2 (3.9)		
Liver transplant indication, compensated cirrhosis with HCC	1 (2.3)	4 (7.8)	**0.35 (0.13-0.93)**	**0.035**
Diabetes	13 (29.5)	17 (33.3)	0.91 (0.52-1.59)	0.740
Arterial hypertension	18 (40.9)	30 (58.8)	1.37 (0.80-2.36)	0.260
History of ascites	26 (59.1)	45 (88.2)	**3.26 (1.44-7.39)**	**0.005**
Refractory ascites	2 (4.5)	4 (7.8)	1.39 (0.55-3.54)	0.490
History of encephalopathy	18 (40.9)	27 (52.9)	1.55 (0.90-2.65)	0.110
History of variceal bleeding	14 (31.8)	12 (23.5)	0.84 (0.44-1.58)	0.580
Primary prophylaxis of CSPH	14 (31.8)	18 (35.3)	0.85 (0.49-1.46)	0.550
History of spontaneous infections	8 (18.2)	12 (23.5)	1.46 (0.76-2.79)	0.250
Primary SBP prophylaxis	1 (2.3)	10 (19.6)	**3.40 (1.95-5.92)**	**<0.001**
Leukocytes (10^9/L)	4.72 (3.21-6.22)	4.02 (3-5.79)	1 (0.99-1)	0.0997
Platelets (10^9/L)	98 (75-145.65)	72 (56.9-128)	**0.99 (0.98-0.99)**	**0.014**
AST (IU/L)	36 (26-60)	40 (21-61)	1.01 (0.99-1.01)	0.081
ALT (IU/L)	35 (18-77)	22 (16-47)	1.00 (0.99-1.01)	0.195
Bilirubin (mg/dl)	1.49 (0.87-2.24)	2.70 (1.52-7.08)	**1.08 (1.05-1.10)**	**<0.001**
INR	1.42 (1.21-1.67)	1.66 (1.43-2.09)	**1.99 (1.32-2.99)**	**0.001**
Albumin (g/dl)	3.30 (2.92-3.49)	2.79 (2.34-3.16)	**0.54 (0.35-083)**	**0.004**
Urea (mg/dl)	29 (22-38)	37 (25-61)	**1.02 (1.02-1.03)**	**<0.001**
Na (mmol/L)	137 (134-139)	134 (131-136)	**0.92 (0.87-0.97)**	**0.003**
Creatinine (mg/dl)	0.70 (0.56-0.90)	1.10 (0.69-1.40)	**2.43 (1.83-3.23)**	**<0.001**
CysC (mg/L)	0.98 (0.83-1.29)	1.56 (1.50-2.06)	**2.67 (1.96-3.64)**	**<0.001**
eGFR (ml/min/1.73 m^2)	106 (77-146)	67 (53-99)	**0.98 (0.97-0.99)**	**<0.001**
Child-Pugh score	7 (6-8)	10 (8-11)	**1.31 (1.16-1.47)**	**<0.001**
MELD-Na	13 (9-18)	22 (18-27)	**1.13 (1.09-1.16)**	**<0.001**
MELD-CysC	11 (6-13)	17 (14-21)	**1.16 (1.12-1.20)**	**<0.001**
MELD 3.0	14 (10-19)	22 (18-28)	**1.14 (1.10-1.18)**	**<0.001**
GEMMA NA	14 (12-18)	23 (18-27)	**1.15 (1.09-1.21)**	**<0.001**
MELD sarcopenia	16 (10-20)	28 (25-33)	**1.12 (1.09-1.15)**	**<0.001**
Subjective global assessment				
A	23 (52.3)	10 (19.6)		
B	14 (31.8)	24 (47.1)	**1.88 (1.31-2.71)**	**0.001**
C	7 (15.9)	17 (33.3)		
Visceral adipose tissue index (cm^2/m^2) (n = 100)	44.92 (23.50-73.65)	40.96 (31.11-52.10)	**0.98 (0.97-0.99)**	**<0.001**
Subcutaneous adipose tissue index (cm^2/m^2) (n = 100)	67.49 (43.02-82.24)	59.51 (35.59-91.35)	1.01 (0.99-1.01)	0.531
Visceral subcutaneous ratio (n = 100)	0.91 (0.45-1.42)	0.56 (0.43-0.94)	0.71 (0.38-1.32)	0.280
Visceral obesity (n = 100)	8 (21.6)	7 (18.4)	0.94 (0.43-2.09)	0.870
Skeletal Muscle Index (cm^2/m^2) (SMI)	46.66 (39.94-52.69)	41.53 (36.99-48.3)	**0.96 (0.93-0.99)**	**0.013**
Sarcopenia by SMI	14 (31.8)	44 (86.3)	**5.34 (2.48-11.53)**	**<0.001**
Sarcopenic visceral obesity (n = 100)	5 (13.5)	7 (18.4)	1.13 (0.51-2.50)	0.770
Average feather index (cm^2/m^2)	0.83 (0.70-0.93)	0.70 (0.47-0.83)	**0.16 (0.04-0.63)**	**0.009**
Average compression index (cm^2/m^2)	0.33 (0.29-0.39)	0.22 (0.18-0.35)	**0.06 (0.04-0.63)**	**0.033**
Sarcopenia HIBA score	-1.43 (-2.57 to -0.43)	0.10 (-1.90 - 1.14)	**1.19 (1.01-1.39)**	**0.035**
6-min walk test (meters) (n = 105)	230 (196-342)	196 (130-266)	**0.98 (0.98-0.99)**	**0.002**
Hand grip strength (average) (n = 115)	53.33 (38.67–68.66)	39.67 (26.67-53.33)	**0.98 (0.96-0.99)**	**0.009**
Liver Frailty Index (numeric) (n = 115)	3.00 (2.31-3.70)	3.90 (3.33-4.28)	**1.92 (1.31-2.81)**	**<0.001**
Liver Frailty Index Score (categorized) (n = 115)				
Robust	25 (59.5)	9 (23.7)	Ref.	
Pre-frail	14 (33.3)	23 (60.5)	**2.78 (1.32-5.85)**	**0.007**
Frail	3 (7.1)	6 (15.8)	**3.29 (1.19-9.07)**	**0.021**

ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; HIBA, Hospital Italiano de Buenos Aires; INR, international normalized ratio; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; SBP, spontaneous bacterial peritonitis; sHR, subdistribution hazard ratio; SMI, skeletal muscle index; WL, waiting list.
Fine and Gray competing risk regression analysis was performed, considering liver transplantation and death as the competing risks for acute-on-chronic liver failure in patients on the waiting list.

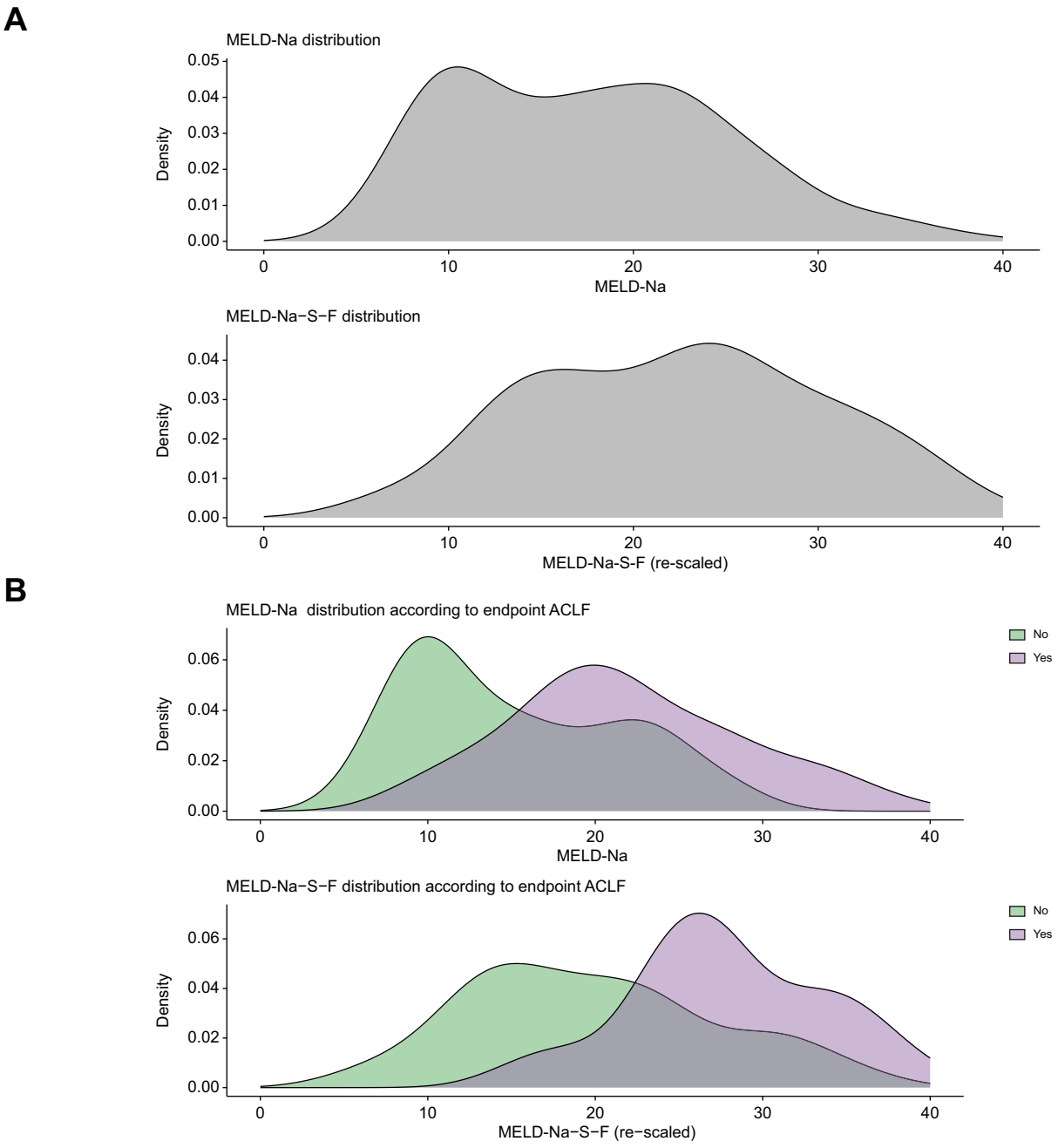

Fig. 3. Comparison between MELD-Na and MELD-Na-sarcopenia-LFI. (A) Distribution of individual scores. (B) Discrimination between patients with and without ACLF for the two scores according to the development of ACLF. ACLF, acute-on-chronic liver failure; MELD-Na, model for end-stage liver disease-sodium.

on applicability (Fig. S1). The correlation between the different tools was moderate to poor. Despite this, the AUROC of the sarcopenia HIBA score to determine the presence of sarcopenia was 0.77 (0.70-0.85) p <0.001, like that reported in previous studies.[9] The fact that muscle is a common factor between sarcopenia and frailty implies that there is an overlap between these conditions and the factors that contribute to their development.[4] Loss of muscle function can lead to loss of muscle mass and vice versa. However, these conditions can occur in isolation and determine an independent risk of unfavorable outcomes, which indicates that they capture different phenotypes within the same syndrome of low physiological functional reserve.[31] Our results are consistent with those of previous studies in which both sarcopenia and frailty were evaluated in the same study.[12,32,33] The bidirectional relationship between these conditions is plausible, especially in scenarios where both share predisposing factors such as anorexia, ascites, hepatic encephalopathy, and proinflammatory states with the release of cytokines that can lead to increased energy consumption, reduced nutritional intake, and physical inactivity, with the consequent increased risk of developing or worsening the presence of sarcopenia and frailty.[4] Nevertheless, new studies that allow for a better

Table 4. Main characteristics at ACLF, and its association with mortality on the WL for LT.

Characteristics at ACLF	Alive n (%)/median (IQR)	Death n (%)/median (IQR)	sHR (95% CI)	*p* value
Sex, male	5 (71.4)	18 (85.7)	2.55 (0.68-9.52)	0.164
BMI (kg/m^2)	24 (23-28)	28 (25-30)	0.98 (0.91-1.05)	0.566
Subjective global assessment				
A	0	5 (23.8)		
B	3 (42.9)	8 (38.1)	1.05 (0.45-2.05)	0.891
C	4 (57.1)	8 (38.1)		
Subcutaneous adipose tissue index (cm^2/m^2) (n = 38)	51.04 (23.71-69.50)	60.58 (44.24-101.67)	0.99 (0.98-1.01)	0.951
Visceral adipose tissue index (cm^2/m^2) (n = 38)	28.24 (14.77-41.32)	45.85 (31.11-63.68)	1.02 (0.98-1.05)	0.281
Visceral subcutaneous ratio (n = 38)	0.44 (0.41-1)	0.72 (0.38-0.94)	0.94 (0.55-1.62)	0.832
Visceral obesity (n = 38)	0	3 (20)	0.99 (0.31-3.20)	0.997
Sarcopenia by SMI	7 (100)	19 (90.5)	1.56 (0.32-7.51)	0.578
Sarcopenic visceral obesity (n = 38)	0	3 (20)	0.99 (0.31-3.20)	0.997
Sarcopenia HIBA score	0.61 (-1.67 - 1.21)	0.27 (0.81-1.14)	1.15 (0.92-1.44)	0.224
Average feather index cm^2/m^2	0.57 (0.44-0.79)	0.71 (0.53-0.88)	7.16 (0.94-54.51)	0.60
Average compression index cm^2/m^2	0.21 (0.18-0.31)	0.27 (0.19-0.36)	4.95 (0.38-64.52)	0.222
Liver frailty index (numeric) (n = 38)	3.26 (2.75-4.28)	3.93 (3.72-4.47)	2.03 (0.79-5.26)	0.143
Liver frailty index score (categorized) (n = 38)				
Robust	3 (42.9)	3 (18.8)		
Pre-frail	3 (42.9)	9 (56.3)	2.13 (0.76-5.95)	0.148
Frail	1 (14.3)	4 (25)		
6-min walk test (meters) (n = 32)	210 (120-322)	161 (107.5-280)	0.99 (0.99-1.01)	0.093
Hand grip strength (average) (n = 38)	62.67 (24-83.33)	35.67 (24.17-51.67)	0.98 (0.95-1.02)	0.387
Triggering event				
Variceal bleeding	0	0	1.11 (0.85-1.43)	0.452
Infection	4 (57.1)	13 (61.9)		
Hepatic encephalopathy	0	0		
No precipitating event	3 (42.9)	8 (38.1)		
Type of infection				
Urinary tract infection	1 (25)	1 (7.7)		
SBP	0	6 (46.2)		
Pneumonia	2 (50)	0		
Spontaneous bacteremia	0	1 (7.7)	1.22 (0.99-1.5)	0.060
Cellulitis	0	0		
Cholangitis	0	0		
COVID-19	1 (25)	5 (38.5)		
Leukocytes (10^9/L)	5.63 (4.68-8.99)	5.93 (3.02-7.59)	**1.10 (1.09-1.11)**	**0.029**
Platelets (10^9/L)	12.3 (45.6-144.4)	56.4 (45.2-75.5)	0.99 (0.9-1.11)	0.240
Bilirubin (mg/dl)	2.30 (1.69-2.88)	4.9 (2.32-8)	0.98 (0.94-1.01)	0.245
INR	2.1 (1.52-2.36)	1.78 (1.6-2.2)	0.74 (0.50-1.10)	0.139
Albumin (g/dl)	2.45 (2.34-3.24)	2.5 (2.28-2.96)	0.74 (0.36-1.54)	0.423
Creatinine (mg/dl)	2.01 (2-2.34)	2.10 (1.90-2.48)	1.13 (0.80-1.61)	0.481
Na (mmol/L)	131 (129-135)	133 (130-138)	1.06 (0.93-1.21)	0.351
CLIF-C ACLF	44 (37-51)	48 (40-60)	**1.07 (1.01-1.13)**	**0.018**
MELD-Na	27 (23-29)	27 (24-31)	0.99 (0.93-1.07)	0.955
MELD 3.0	29 (22-30)	29 (23-31)	0.99 (0.93-1.06)	0.861
MELD sarcopenia	33 (31-38)	34 (30-36)	1.01 (0.95-1,06)	0.905
Organic dysfunction				
Renal	2 (28.6)	4 (19)	1.12 (0.72-1.74)	0.613
Neurological	5 (71.4)	9 (42.9)		
Both	0	0		
Kidney failure	5 (71.4)	14 (66.7)	2.08 (0.83-5.22)	0.117
Coagulation failure	2 (28.6)	3 (14.3)	2.08 (0.83-5.22)	0.338
Liver failure	0	7 (33.3)	0.98 (0.39-2.5)	0.969
Brain failure	1 (14.3)	9 (42.9)	**3.66 (1.48-9.04)**	**0.005**
Circulatory failure	0	10 (47.6)	**3.53 (1.46-8.50)**	**0.005**
Respiratory failure	0	7 (33.3)	**38.68 (11.36-131.65)**	**<0.001**
ACLF grade				
1	6 (85.7)	9 (42.9)	**2.96 (1.69-5.19)**	**<0.001**
2	1 (14.3)	3 (14.3)		
3	0	9 (42.9)		

ACLF, acute-on-chronic liver failure; HIBA, Hospital Italiano de Buenos Aires; INR, international normalized ratio; LT, liver transplantation; MELD, model for end-stage liver disease; sHR, subdistribution hazard ratio; SMI, skeletal muscle index; WL, waiting list.
Fine and Gray competing risk regression analysis was conducted, considering liver transplantation as the competing risk for death in patients on the waiting list.

understanding of the granularity of the mechanisms involved in sarcopenia and frailty, as well as why they capture different risks, are necessary.

The development of ACLF represents a crucial event in the natural history of cirrhosis and is characterized by high short-term mortality.[34] The main treatment for this syndrome is LT.[35] Despite this, as ACLF is characterized by the development of multiple organ failures, it can threaten the transplantability of patients and increase WL mortality.[36,37] In our study, 39% of the patients developed ACLF, with a 41% mortality rate on the WL. The presence of more advanced liver disease (MELD-Na), frailty by LFI, and sarcopenia by SMI were independent predictive factors for the development of ACLF on the WL. Our model was constructed using various tools to assess sarcopenia and frailty, and the fact that both LFI and sarcopenia by SMI emerged as independent factors not only highlights the significance of both but also underscores that they capture distinct phenotypes and thus may be complementary. In cases where frailty assessment was not feasible, it is notable that a high percentage of these patients were sarcopenic. While previous studies have shown that the presence of sarcopenia or frailty is an independent predictor of ACLF on the WL for LT, [16,38] combining the assessment of both parameters using objective tools provides a better understanding of ACLF risk. Indeed, adding both assessment tools to the MELD-Na significantly improved discriminative capacity.

The need to improve the characterization of patients with a higher risk of developing ACLF is related to the possibility of applying therapeutic strategies that mitigate this lower functional reserve and consequently decrease the risk of developing ACLF. Therefore, the presence of sarcopenia and frailty represents a potential predisposing factor for progression in the natural history of cirrhosis, and an early identification of at-risk patients might help not only in the prevention of ACLF but also in the success of treatment strategies.

The cornerstone of treating sarcopenia and frailty is moderate-intensity physical activity (both aerobic and resistance) and optimizing nutritional intake (adequate daily energy intake, meeting protein intake, increasing meal frequency, and avoiding prolonged fasting with a late evening snack).[3] The use of potential nutritional supplements, such as branched-chain amino acids,[39] and intramuscular administration of testosterone are a potential therapeutic strategy.[40] Undoubtedly, early and large-scale treatment interventions for sarcopenia and frailty in cirrhosis are key to improving patient prognosis and quality of life. Despite this, well-designed clinical trials in patients with different stages of cirrhosis are required to verify the impact of improvement in sarcopenia and frailty.

Lastly, our study showed that in patients with ACLF, the development of a greater number of organ failures, especially respiratory and circulatory failure, as well as a greater degree of systemic inflammation, are the main determinants of mortality on the WL for LT.[29,36,41] Conversely, the impact of sarcopenia or frailty and MELD-Na in these instances does not appear to be a determining factor in mortality once ACLF is established, which reinforces the need for these entities to be addressed early. Our results are in contrast with those recently published by Rio *et al.* regarding the effects of sarcopenia in patients with ACLF.[42] However, the fact that our cohort was limited to patients on the WL for LT and considered LT as a competing risk for mortality may explain the differences in prognostic value.

The findings of this study should be considered in light of several limitations. Given our interest in identifying the impact of various objective metrics to assess sarcopenia and frailty in a selective population of patients entering the WL for LT, our relatively small sample size may have resulted in overfitting of our model, which might not reflect the broader population of patients with cirrhosis, limiting the generalizability of our findings. Annual recruitment was higher in previous studies from our LT unit,[9,16,43] owing to the impact of the COVID-19 pandemic, which not only affected recruitment but also exposed our cohort to COVID-19 as a potential trigger for the development of ACLF or post-LT mortality. However, the prevalence of malnutrition, visceral obesity, and sarcopenia in our study population was similar to that reported in previous studies, which included a larger and more heterogeneous cohort of patients with cirrhosis awaiting LT,[1,7] though the prevalence of frailty was lower than that reported in other studies. We understand that this may be related to the severity of the included patients (*e.g.*, the percentage of patients with hepatic encephalopathy) and even the prevalence of females.[31] Despite this, it is interesting to note that the cut-off points were established in different geographic areas, and our results may reflect this. Finally, when analyzing the median LFI, it was very similar to that expressed in studies of similar characteristics.[44] Another possible limitation was the inclusion of a subgroup of patients with compensated cirrhosis, in whom HCC was the indication for LT, in the analysis of the development of ACLF. However, this subgroup of patients was not exempt from developing ACLF on the WL and, in fact, 4/17 (23.5%) developed ACLF on the WL. Lastly, it is important to emphasize that only two patients who developed ACLF simultaneously were evaluated, and their exclusion did not impact the results. Another limitation is the lack of a history of previous ACLF episodes before inclusion on the WL.

In conclusion, our results confirm that sarcopenia and frailty are two different sides of the same coin and are independent predictors of the development of ACLF on the WL for LT. Similarly, the assessment of the presence of sarcopenia by SMI and frailty by LFI helps refine the predictive capacity of MELD-Na on the LT WL, thus allowing us to determine early treatment interventions that are not only more effective but also more important to prevent the progression of cirrhosis. Finally, further studies are needed to explore the pathophysiological mechanisms of sarcopenia and frailty that independently or synergistically promote or facilitate the progression of cirrhosis.

Abbreviations

6MWT, 6-minute walk test; ACLF, acute-on-chronic liver failure; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; HGS, hand grip strength; HIBA, Hospital Italiano de Buenos Aires; HR, hazard ratio; LFI, liver frailty index; LT, liver transplant; MELD(-Na), model for end-stage liver disease(-sodium); SAT, subcutaneous adipose tissue; SGA, subjective global assessment; sHR, subdistribution hazard ratio; SMI, skeletal muscle index; VAT, visceral adipose tissue; US, ultrasound; WL, waiting list.

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Conflicts of interest

All authors declare no conflicts of interest for this study.

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

Authors' contributions

GGP: acquisition of data; interpretation of data; writing manuscript. JCS: acquisition of data interpretation of data; writing manuscript. JM: acquisition of data, critical revision of the manuscript. LS: acquisition of data, critical revision of the manuscript. MB: acquisition of data, critical revision of the manuscript. SB: acquisition of data, critical revision of the manuscript. MP: acquisition of data, critical revision of the manuscript. EGC: analysis and interpretation of data, critical revision of the manuscript. VMG: analysis and interpretation of data, critical revision of the manuscript. MDS: interpretation of data, critical revision of the manuscript. SM: interpretation of data, critical revision of the manuscript. EDS: interpretation of data, critical revision of the manuscript. AG: interpretation of data, critical revision of the manuscript. JP: interpretation of data, critical revision of the manuscript. JGA: analysis and interpretation of data; writing of the manuscript, study concept and design. EM: acquisition; data analysis and interpretation; manuscript writing, study concept and design.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author (EM).

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100985.

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