ORIGINAL ARTICLE

Sarcopenia HIBA score predicts sarcopenia and mortality in patients on the liver transplant waiting list

Ezequiel Mauro[1,2] | Juan Manuel Diaz[1] | Lucrecia Garcia-Olveira[1] | Juan Carlos Spina[2,3] | Lorena Savluk[2,3] | Fernanda Zalazar[1] | Julia Saidman[3] | Martin De Santibañes[2] | Juan Pekolj[2] | Eduardo De Santibañes[2] | Gonzalo Crespo[4] | Juan G. Abraldes[5] | Adrían Gadano[1,2]

[1]Liver Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[2]HPB and Liver Transplant Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[3]Radiology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[4]Liver Transplant Unit, Liver Unit, IDIBAPS, CIBERehd, Hospital Clínic, University of Barcelona, Barcelona, Spain

[5]Division of Gastroenterology, University of Alberta, CEGIIR, Edmonton, Alberta, Canada

Correspondence
Ezequiel Mauro M.D., MSc., Liver Unit & Liver Transplant Unit, Hospital Italiano de Buenos Aires, Perón 4190, C1199 ABH, Buenos Aires, Argentina.
Email: ezequiel.mauro@hiba.org.ar

Abstract

Sarcopenia is a prevalent condition that predicts prognosis in patients awaiting liver transplantation (LT). The gold standard for the diagnosis of sarcopenia is the assessment of the muscular area at L3 with computed tomography (CT) scan (skeletal muscle index [SMI]), but the routine use of CT scan is limited in clinical practice. Thus, we designed a single-center observational study aimed to evaluate the clinical factors associated with the presence of sarcopenia by SMI, and to build a score capable of predicting or excluding the presence of sarcopenia in patients on the LT waiting list (WL). Binary logistic regression analysis was performed to establish the factors independently associated with sarcopenia, and the Sarcopenia Hospital Italiano de Buenos Aires (HIBA) score was built from the resulting model after internal validation analysis by bootstrapping and correction for optimism. The predictive capability of mortality on the WL was evaluated with competing risk regression analysis. A total of 215 patients with cirrhosis on the LT WL were included. The independent factors associated with the presence of sarcopenia were male sex (odds ratio [OR]: 6.09, $p < 0.001$), body mass index (OR: 0.74, $p < 0.001$), Child Pugh (OR: 1.44, $p < 0.001$), and the ratio creatinine/Cystatin C (OR: 0.03, $p = 0.007$). The Sarcopenia HIBA score constructed with these variables showed an area under the curve of 0.862. During follow-up, 77 (36%) patients underwent LT, 46 (21%) died, and 92 (43%) remained alive. After adjusting for Model for End-Stage Liver Disease–Sodium, Sarcopenia HIBA score was an independent predictor of WL mortality (subhazard ratio: 1.19; 95% confidence interval 1.01–1.40; $p = 0.042$). Sarcopenia HIBA score is an easy-to-use, objective, and reliable diagnostic and predictive tool that can be useful to improve the prognostic evaluation and allow identifying a group of patients with a higher risk of death while awaiting LT.

INTRODUCTION

The prognosis of cirrhosis is determined by the conjunction of several factors: liver function (bilirubin, prothrombin time [international normalized ratio] and albumin), complications of portal hypertension (ascites, encephalopathy, hyponatremia), and extrahepatic organs involvement (creatinine).[1] Recently, it has been shown that the presence of sarcopenia is an independent predictor of mortality in patients on the waiting list (WL) for liver transplant (LT).[2,3]

Sarcopenia is defined as the total or functional loss of muscle mass, and is generally associated with high rates of complications, such as susceptibility to infections, hepatic encephalopathy, ascites, development of acute-on-chronic liver failure (ACLF), and even a significant increase in mortality in patients on the WL for LT, independently from Model for End-Stage Liver Disease (MELD) or MELD-Na scores.[3–6] The presence of sarcopenia is between 20% and more than 40% in patients with compensated and decompensated cirrhosis, respectively.[6] Sarcopenia represents the presence of a lower functional physiological reserve against an injury, which conditions a greater risk of adverse events.[7] As a consequence, cirrhosis can be considered as a state of accelerated physiological aging process, in which multiple factors inherent to complications of the liver disease (encephalopathy, infections, ascites) are clearly related to the development of sarcopenia, but, at the same time, perpetuate and aggravate the critical state of the muscle mass.[2,6]

The gold standard for the diagnosis of sarcopenia is the assessment of the muscle area at L3 by means of a computed tomography (CT).[7] The abdominal skeletal area at L3 is normalized according to height, to calculate the skeletal muscle index (SMI: cm^2/m^2), and the existence of sarcopenia is determined according to gender (women < 39 cm^2/m^2 and men < 50 cm^2/m^2).[2] The routine use of CT scans, particularly if repeated over time, is limited in clinical practice due to the cost, radiation exposure, and the need for specialized interpretation. Therefore, new tools for nutritional screening and monitoring of such condition over time would be required. In this scenario, recent studies have shown that the efficacy of a clinical screening tool for malnutrition such as the subjective global assessment (SGA), bioelectrical impedance analysis (BIA), or dual-energy X-ray absorptiometry (DXA) were unsatisfactory in the setting of WL for LT, raising the need of new tools to optimize the prediction of this condition.[8–10]

Cystatin C (CysC) is a low molecular weight protein, which after glomerular filtration is fully catabolized in the proximal renal tubule and is not returned to blood. CysC has been proposed as an alternative biomarker to estimate renal function, because it does not appear to be affected by patients' muscle mass, protein deficiency, gender disparity, or hyperbilirubinemia.[11] In patients with cirrhosis, CysC predicts acute kidney injury (AKI), chronic kidney disease (CKD), ACLF, and mortality on the WL.[3,12–14] In addition, in different settings such as critically ill patients,[15–17] colon cancer,[18] aging population,[19,20] CKD,[21] diabetes[22,23] and transplantation,[24,25] the creatinine/CysC ratio has proven to be a reliable and reproducible parameter with an adequate diagnostic capacity to predict the presence of sarcopenia.[26] However, the evidence in patients with cirrhosis is scarce.[27,28] In this setting, our objective was to evaluate the factors associated with the presence of sarcopenia (particularly including the creatinine/CysC ratio), and to build a score capable of predicting its presence in patients awaiting LT, as well as to evaluate the capacity of such score as a predictor of mortality.

MATERIALS AND METHODS

Patients

This is a single-center observational study in which all consecutive patients with cirrhosis in the WL for LT (January 2014 to April 2019) at the Hospital Italiano de Buenos Aires (HIBA) were included. All variables, including the presence of sarcopenia by CT, were collected at the time of the inclusion on the WL. Patients were followed from the inclusion in the WL to death, LT, or last date of follow-up. We excluded patients with HCC outside the Milan criteria, patients without evidence of cirrhosis as determined by clinical or histological methods, those with active extra-hepatic neoplasia, simultaneous liver-kidney transplant and listed for liver re-transplantation, and patients in whom SMI or CysC were not assessed.

Baseline assessments at WL inclusion

Data were collected at the time of listing for LT. We obtained data related to comorbidities (body mass index [BMI], arterial hypertension, and diabetes] and liver disease (etiology, LT indication, history of decompensation, and laboratory tests). In addition, at this same time point, we evaluated renal function by different methods: evidence of AKI and CKD at the time of WL inclusion,[29] serum levels of CysC (Human CYSTATIN C Kit, SPAplus; Binding Site Group, Birmingham, UK) and estimated glomerular filtration rate (eGFR) by modification of diet in renal disease (MDRD-6).[30] Finally, sarcopenia assessment was performed by CT skeletal muscle index at L3 level.[31] Although CT scan (used for muscle mass evaluation) was performed as standard of care during LT assessment, it did not constitute a mandatory part of our LT evaluation protocol.

Study definitions

- SMI: We used CT at the third lumbar vertebrae (L3), performed within 3 months before listing, and analyzed with Alma Medical Imaging 4.2.0.25 (ALMA IT Systems 2005–2014). A transverse CT image from L3 in the inferior direction was assessed from each scan. Skeletal muscle was identified and quantified, and the cross-sectional area of the muscle and adipose tissue was normalized for height (cm^2/m^2), as reported in previous studies. Muscles in the L3 region include psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. All CT scans were analyzed by a junior (J.S.) and 2 senior (L.S. and J.C.S.) radiologists, who were blinded to the outcome. The SMI was expressed as cross-sectional L3 muscle area/height^2.[31,32]
- *AKI at WL inclusion:* Defined by an increase in creatinine by ≥ 0.3 mg/dL within 48 hours or a percentage increase in creatinine by ≥ 50% from baseline, which is known or presumed to have occurred within the prior 7 days.[29]
- *CKD at WL inclusion:* Defined when the eGFR estimated by MDRD6 was < 60 mL/min/1.73 m^2 in at least two consecutive determinations separated at least by 3 months.[30]
- *Ratio creatinine/CysC:* Defined from the serum levels of creatinine and CysC, used as a biomarker associated with sarcopenia.

Evaluation of outcomes

- *Sarcopenia:* Defined according to the following cutoff values: L3 SMI: <39 cm^2/m^2 for women and <50 cm^2/m^2 for men.[31,32]
- *Mortality on WL:* Mortality within the WL period was evaluated. For this outcome, patients were followed until death, transplantation, or date of last follow-up.

Statistical analysis

Median and interquartile range (IQR) were used to describe quantitative variables and number of cases and percentages for qualitative variables. The differences between the qualitative variables were compared using the chi square test or Fisher's exact test when indicated. Quantitative variables were analyzed with non-parametric tests (Mann-Whitney or Kruskal-Wallis for unpaired samples). A binary logistic regression analysis was performed to establish the factors independently associated with sarcopenia. Because our hypothesis stipulates evaluating the creatinine-CysC ratio as an objective predictor of sarcopenia,[26] we decided to prespecify the inclusion of the ratio in the model, as a clinically relevant variable, independent of the interpretation of the unadjusted analysis. The association is presented as odds ratio (OR) and 95% confidence intervals (CIs). The Sarcopenia HIBA score was built from the resulting model, with internal validation and correction for optimism with bootstrapping. This has been shown to be a more efficient procedure than sample splitting.[33] Model was tested for discrimination (c-statistic or area under receiver operating characteristic curve) and calibration by plotting predicted versus observed probabilities with Loess calibration. Score thresholds were established according to 20th and 80th percentile of sarcopenia HIBA score to rule in or out sarcopenia. We analyzed the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, correctly classified patients, positive predictive value, and negative predictive value. A nomogram was built to predict the presence of sarcopenia based on the sarcopenia HIBA score.

Fine and Gray competing risk regression analysis (with LT as the competing risk of mortality in WL) and multivariable Cox regression analysis of cause-specific hazards was performed to evaluate variables associated with the mortality on the WL. Estimated risks are presented as subhazard ratios (sHRs) and hazard ratios (HRs), respectively, with 95% CI. Variables with a *p* value ≤ 0.1 at univariate analysis as well as those considered clinically significant were included in multivariate analyses. All tests were two-tailed, and a *p* value < 0.05 was considered statistically significant. SPSS version 26 and R (version 3.5.1) were used to perform the statistical analysis.

RESULTS

Patients

A flow chart of the study is shown in Figure 1. A total of 215 patients were included. The main characteristics of the patients are found in Supporting Table S1. The prevalence of sarcopenia was 43%.

Factors associated with sarcopenia and accuracy of the sarcopenia HIBA score

The median time between the image and the admission in the WL for LT was 2 (1–37) days. On univariate analysis (Table 1), the factors associated with sarcopenia in the WL were male gender, low BMI, the etiology of cirrhosis, history of ascites, history of encephalopathy, high values of leukocytes, alkaline phosphatase and bilirubin, hypoalbuminemia, elevated CysC values, hyponatremia, and higher value of Child Pugh and MELD-Na scores. In multivariable analysis, the factors independently associated with the
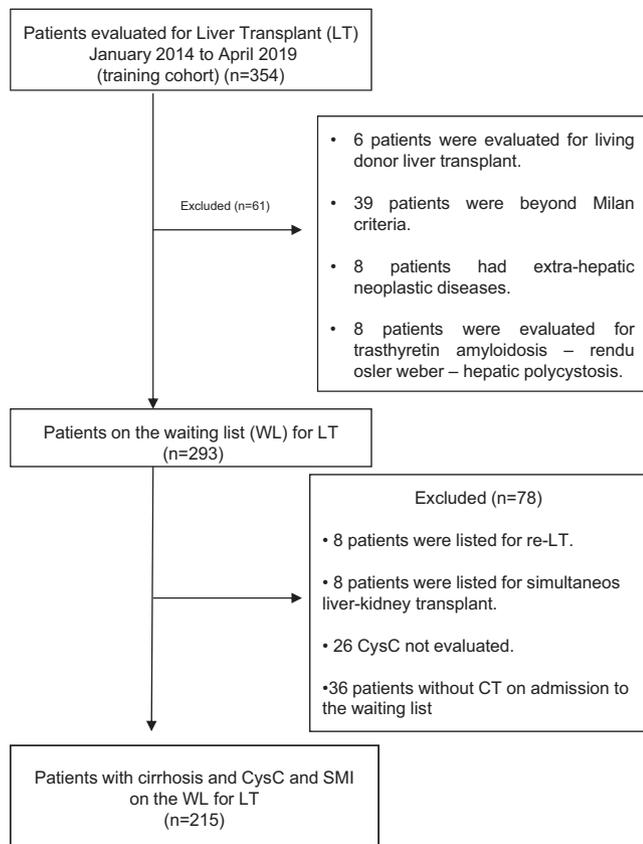
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Patients evaluated for Liver Transplant (LT)
January 2014 to April 2019
(training cohort) (n=354)
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Excluded (n=61)
- 6 patients were evaluated for living donor liver transplant.
- 39 patients were beyond Milan criteria.
- 8 patients had extra-hepatic neoplastic diseases.
- 8 patients were evaluated for trasthyretin amyloidosis – rendu osler weber – hepatic polycystosis.

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Patients on the waiting list (WL) for LT
(n=293)
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Excluded (n=78)
- 8 patients were listed for re-LT.
- 8 patients were listed for simultaneos liver-kidney transplant.
- 26 CysC not evaluated.
- 36 patients without CT on admission to the waiting list

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Patients with cirrhosis and CysC and SMI
on the WL for LT
(n=215)
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FIGURE 1 Flowchart of the patients included in the study

presence of sarcopenia were male gender (OR: 6.09, 95% CI 2.53–14.63, $p < 0.001$), BMI (OR: 0.74, 95% CI 0.67–0.81, $p < 0.001$), Child Pugh (OR: 1.44, 95% CI 1.20–1.73, $p < 0.001$), and the Creatinine/CysC ratio (OR: 0.03, 95% CI 0.003–0.40, $p = 0.007$). Finally, the bootstrap-corrected prediction model was Sarcopenia HIBA score = Male × 1.707 + BMI × (−0.290) + Child Pugh × (0.346) + Creatinine/CysC × (−3.193) + 5.5. Figure 2 presents the probability of presenting sarcopenia as a function of the different components of the Sarcopenia HIBA score, and Supporting Figure S1 represents the weight of the contribution of each of the components to the predictive value of the score.

Regarding the accuracy of the Sarcopenia HIBA score, the area under the curve (AUC) was 0.862 (95% CI 0.814–0.91, $p < 0.001$), and the capacity of the Sarcopenia HIBA score to differentiate the subpopulations of patients with or without sarcopenia is graphically presented in Figure 3. The 20th (−2.09) and 80th (1.17) percentile values for the Sarcopenia HIBA score were used as threshold, and Table 2 lists the main measures of diagnostic accuracy of the score. Finally, to individualize the risk, a predictive nomogram for sarcopenia was created with these four variables (Figure 4).

Finally, given that in the setting of advanced liver disease and fluid overload, the use of BMI may lead to underestimation of the presence of sarcopenia and overestimation of that of obesity, we assessed the

correlation of the observed BMI with the BMI estimated by dry weight,[34] observing an excellent Pearson correlation of 0.93 ($p < 0.001$; Supporting Figure S2) In addition, in the univariable analysis based on the presence of sarcopenia, the use of BMI or BMI dry weight showed a similar performance for the presence of sarcopenia (Supporting Table S2). This led us to use the standard BMI in the score for simplicity. Regarding sarcopenic obesity (based on a BMI > 30), the use of other variables such as Child Pugh, sex, or an objective parameter with the Creatinine/CysC ratio in the formula, makes the score adjustable to this subgroup (BMI ≥ 30, n = 87 patients; sarcopenia and obesity, n = 15; AUC = 0.702; 95% CI 0.568–836; $p = 0.014$), although with lower performance than that estimated in the whole cohort.

Mortality in patients on the WL

During follow-up, 46 (21%) patients died in the WL, 77 (36%) were transplanted, and 92 (43%) remained alive until the last follow-up. The median follow-up of the patients for the outcome of WL mortality was 11.7 (4.9–25.8) months. On univariate analysis (Table 3), the factors associated with mortality in the WL were gender, history of ascites, history of encephalopathy, history of spontaneous infection, albumin, serum creatinine, serum CysC, Child Pugh score, and MELD-Na score. The presence of sarcopenia by SMI (HR: 5.85, 95% CI 2.90–11.81, $p < 0.001$) and Sarcopenia HIBA score (HR: 1.33, 95% CI 1.15–1.54, $p < 0.001$) were also significantly associated with WL mortality. In multivariable competing risk analysis (considering LT as a competing event for mortality in WL) and after adjusting for MELD-Na, the presence of higher values of Sarcopenia HIBA score (sHR 1.21, 95% CI 1.01–1.45, $p = 0.047$) and MELD-Na (sHR 1.06, 95% CI 1.01–1.11, $p = 0.012$) were independent predictors of WL mortality. Similarly, in the Cox proportional hazard model MELD-Na (HR: 2.66, 95% CI 1.72–4.10, $p < 0.001$) and Sarcopenia HIBA score (HR: 1.76, 95% CI 1.16–2.68, $p = 0.026$) were independently associated with mortality (Figure 5).

DISCUSSION

The presence of sarcopenia in patients awaiting LT is a risk factor for WL mortality,[3,31] postoperative complications,[35] and post-LT death.[36] Although sarcopenia in advanced stages may be readily visible (i.e., "eyeball test"), objective and validated tools are needed to detect the early stages of muscle loss, when therapeutic interventions are likely to modify this entity, and consequently modify the patient's prognosis. In this regard, sex-specific SMI cutoffs by

TABLE 1 Characteristics of the cohort with or without sarcopenia by SMI, on the WL

Characteristics at Inclusion on the WL	Sarcopenia by SMI		p	OR (95% CI) in Multivariable Analysis	p in Multivariable Analysis
	No (n = 122) Count (%)/ Median (IQR)	Yes (n = 93) Count (%)/ Median (IQR)			
Age (years)	60 (53–65)	58 (45–64)	**0.032**		
Gender					
Male	67 (54.9)	66 (71)	**0.016**	**6.09 (2.53–14.63)**	**<0.001**
BMI (kg/m^2)	31 (28–34)	25 (22–28)	**<0.001**	**0.74 (0.67–0.81)**	**<0.001**
BMI classification			**<0.001**		
Normal weight	12 (9.8)	44 (47.3)			
Overweight	38 (31.1)	34 (36.6)			
Class I obesity	45 (36.9)	10 (10.8)			
Class II obesity	16 (13.1)	5 (5.4)			
Class III obesity	11 (9)	0 (0)			
Etiology			**0.011**		
HCV	31 (25.4)	18 (19.4)			
HBV	1 (0.8)	3 (3.2)			
Alcohol	26 (21.3)	22 (23.7)			
NASH	33 (27)	11 (11.8)			
Primary biliary cholangitis	5 (4.1)	5 (5.4)			
Primary sclerosing cholangitis	3 (2.5)	3 (3.2)			
Autoimmune hepatitis	3 (2.5)	11 (11.8)			
Others	20 (16.4)	20 (21.5)			
LT indication			0.137		
Decompensated cirrhosis	100 (82)	83 (89.2)			
Compensated cirrhosis with HCC	22 (18)	10 (10.8)			
Diabetes	52 (42.6)	29 (31.2)	0.086		
Arterial hypertension	40 (32.8)	22 (23.7)	0.143		
History of ascites	82 (67.2)	75 (80.6)	**0.028**		
Refractory ascites	18 (22)	16 (21.3)	0.925		
History of encephalopathy	58 (47.5)	57 (61.3)	**0.045**		
History of variceal bleeding	30 (24.6)	18 (19.4)	0.361		
History of spontaneous infections	20 (16.4)	18 (19.4)	0.573		
Leukocytes (10^9/L)	3.98 (2.97–5.37)	4.55 (3.37–5.77)	**0.049**		
Neutrophil/lymphocyte ratio	1.86 (1.31–2.89)	2.31 (1.69–3.36)	**0.027**		
Platelets (10^9/L)	83.8 (58.5–111.4)	82 (56.7–116)	0.732		
AST (IU/L)	42.5 (30–53)	51 (33–86)	0.112		
ALT (IU/L)	30 (21–49)	36 (23–58)	0.171		
ALP (IU/L)	113.5 (81–150)	134 (111–190)	**0.001**		
Bilirubin (mg/dL)	1.6 (1.18–2.9)	2.26 (1.40–4.07)	**0.010**		
Albumin (g/dL)	2.9 (2.6–3.30)	2.7 (2.4–3.07)	**0.007**		
INR	1.55 (1.4–1.81)	1.65 (1.38–1.87)	0.253		
Creatinine (mg/dL)	0.78 (0.58–0.97)	0.83 (0.62–1.19)	**0.024**		

(Continues)

TABLE 1 (Continued)

Characteristics at Inclusion on the WL	Sarcopenia by SMI		p	OR (95% CI) in Multivariable Analysis	p in Multivariable Analysis
	No (n = 122) Count (%)/ Median (IQR)	Yes (n = 93) Count (%)/ Median (IQR)			
CysC (mg/L)	1.26 (1.02–1.68)	1.55 (1.23–2.09)	**<0.001**		
Creatinine/CysC	0.58 (0.49−0.69)	0.54 (0.44−0.7)	0.159	**0.03 (0.003−0.40)**	**0.007**
Na (mmol/L)	137 (134–139)	135 (132–137)	**0.002**		
eGFR MDRD6 (mL/ min/1.73 m^2)	86 (66–109)	76 (54–106)	0.067		
CKD	3 (2.5)	7 (7.5)	0.105		
Child Pugh			**0.012**		
A	22 (18)	8 (8.6)			
B	61 (50)	38 (40.9)			
C	39 (32)	47 (50.5)			
Child Pugh in number	9 (7–10)	9 (8–11)	**<0.001**	**1.44 (1.20–1.73)**	**<0.001**
MELD-Na	15 (12–19)	17 (15–23)	**0.001**		

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; and NASH, nonalcoholic steatohepatitis.

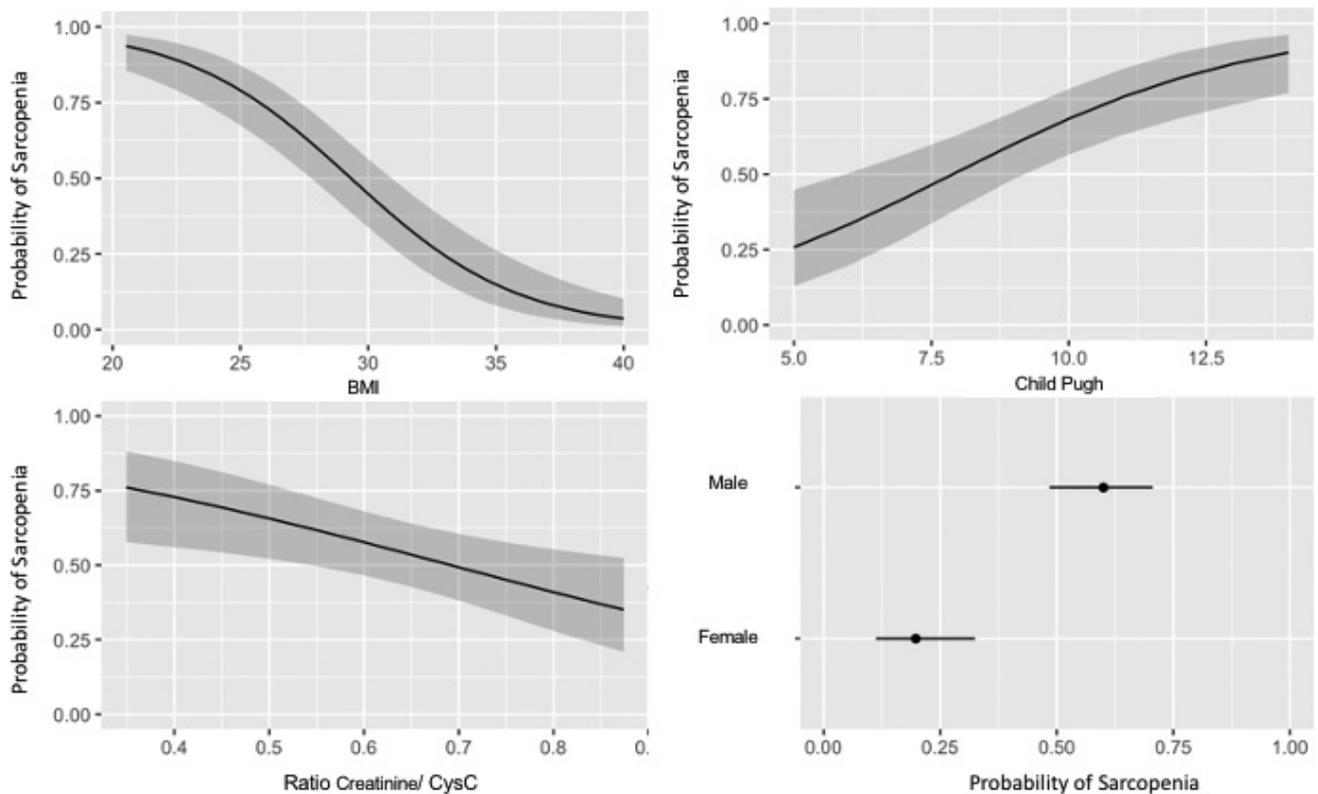They explain the p values that were significant, and the multivariate variables.

FIGURE 2 Probability of sarcopenia as a function of the different components of the sarcopenia HIBA score. The influence of each variable is adjusted by the other three variables

CT scanning are validated and recommended tools for the assessment of sarcopenia.[2] On the other hand, the routine use of CT scan, particularly repeated evaluations to monitor therapeutic measures, are limited in clinical practice due to the high cost, the need for specialized interpretation, and exposure to radiation.[2] Given this clinical setting, our study aimed to investigate the factors associated with the
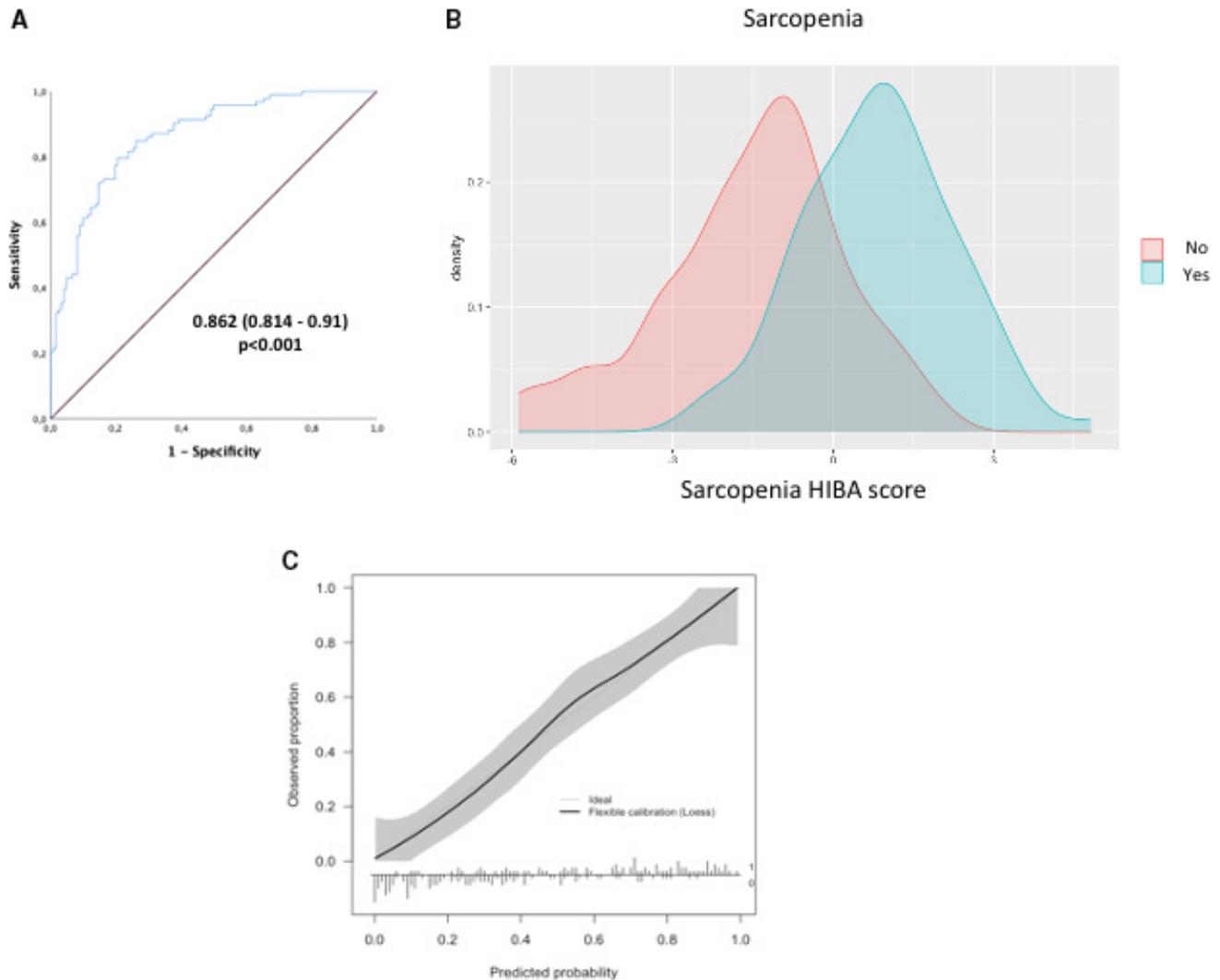
FIGURE 3 (A) Receiver operating characteristic curve to predict sarcopenia with the HIBA score. (B) Distribution of sarcopenia HIBA score distribution in patients with and without sarcopenia. (C) Calibration plot of the HIBA score model to predict sarcopenia. The plot shows an excellent agreement between predicted and observed probabilities of sarcopenia. The line shows the Loess calibration (with 95% CI as the gray area). The histogram at the bottom of the plot shows the distribution of patient with (1) and without (0) sarcopenia

TABLE 2 Accuracy of sarcopenia HIBA score

AUROC (95% CI)	Cutoff for Sarcopenia	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	DOR	CC (%)
0.862 (0.814−0.910)	−2.09	97.8	33.6	52.9	95.3	1.47	0.06	23.03	61.4
$p < 0.001$	1.17	39.8	95.1	86	67.4	8.09	0.63	12.77	71.2

Note: We describe the 20% and 80% percentile thresholds to rule out and rule in Sarcopenia (−2.09 and 1.17, respectively).

Abbreviations: AUROC, area under the receiver operating characteristic curve; CC, percentage of correctly classified patients; LR-, negative likelihood ratio; LR+, positive likelihood ratio; Se, sensitivity; and Sp specificity.

presence of sarcopenia in patients on the WL, and to build a score capable of predicting it.

The Sarcopenia HIBA score is calculated based on sex, BMI, Child-Pugh, and the creatinine/CysC ratio (www.sarcopeniahiba.com). Its strength lies in the excellent ability to predict the presence of sarcopenia in patients on the WL for LT (AUC = 0.862), with a high sensitivity (98%) and specificity (95%) for their cutoff values for the 20th percentile (≤2.09) and 80th percentile (>1.17), respectively. Likewise, high values of the score are independent predictors of mortality in WL, consistent with its ability to predict sarcopenia and its impact in patients on the WL.

Although sarcopenia has traditionally been associated with higher rates of mortality in both men and women with cirrhosis on the WL, recent evidence
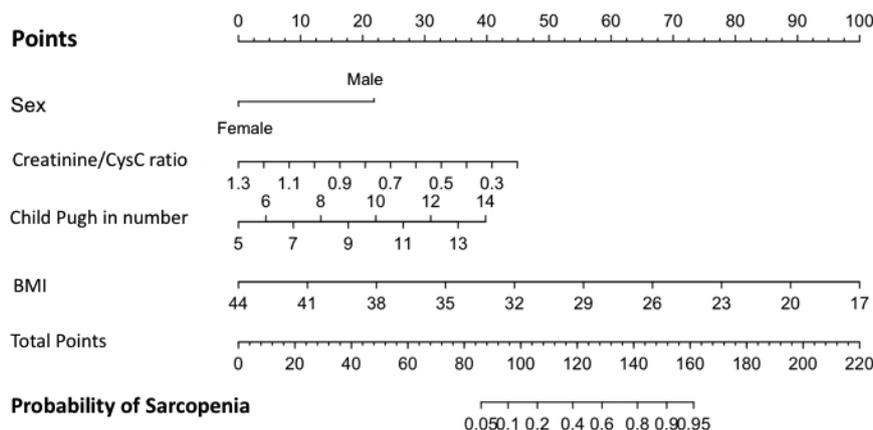
FIGURE 4 Predictive nomogram for sarcopenia in patients awaiting LT

suggests that its prevalence is higher in men, with disproportionately higher mortality rates compared with women.[37] In the same direction, the estimates of nutritional status by anthropometric measures such as BMI is clearly the most important clinical parameter, although it must be highlighted that this parameter is imprecise in the context of ascites. In addition, the presence of sarcopenia is more prevalent in advanced stages of cirrhosis, concordant with the independent predictive value of Child-Pugh stage. Finally, the creatinine/CysC ratio was not significant in the univariate analysis (although its two components were significant alone), but it was an independent determinant of the presence of sarcopenia. This ratio has been extensively studied in multiple clinical settings[15,16,25,17–24] as a possible biomarker of sarcopenia. Lower creatinine/CysC ratio has been associated with lower muscle mass and the higher presence of sarcopenia.[38] In previous studies, the creatinine-to-CysC ratio is tightly correlated with sarcopenia defined by height-indexed skeletal muscle on CT scan.[17,24] It is also strongly correlated with handgrip strength, gait speed, 6-minute walk distances, and is predictive of short-term and long-term survival.[17,19,26] In patients with cirrhosis, serum creatinine is not an adequate kidney biomarker, largely due to the overestimation of the glomerular filtration rate in the presence of sarcopenia.[39] On the other hand, the serum levels of CysC show good performance in the early diagnosis of renal dysfunction in patients with cirrhosis, regardless of muscle mass and gender.[11,40] For these reasons, it is not surprising that this ratio is inversely associated with the presence of sarcopenia, being an objective serological parameter that allows us to adjust the weight of clinical variables such as sex, Child-Pugh score, or BMI.

Our results are important from a clinical point of view. The possibility of having an objective score based on clinical and serological parameters not only facilitates the evaluation as a point of care, but it also makes it possible to optimize "the eye ball" of the treating physician, allowing us to objectify a measurable result over time. Taking into account the need for new treatments that permit modifying this clinical condition, or the possibility to prioritize patients in WL according to their different prognosis, it is mandatory to have a reliable and practical score that allows us to make decisions. In addition, having shown an independent association between high HIBA score punctuation and WL mortality reinforces our results and adds value of the score in clinical practice to optimize prevention and early treatment of patients.

The presence of sarcopenia has recently gained importance as a synonym of a low reserve of physiological response, which carries a low tolerance to decompensating events in the context of advanced cirrhosis.[6] The presence of sarcopenia is one of the main determinant factors associated with a higher risk of ACLF, mortality, or withdrawal from the WL.[3,31,32] Loss of muscle mass can be objectively measured by SMI in clinical practice, and it is less likely to be affected by acute illness or alterations in cognitive function, as can happen with measure of muscle strength or physical performance, which are usually more related to the concept of frailty without showing correlation with SMI.[41] Furthermore, quantification of muscle mass provides objective data, which is especially critical in the setting of WL for LT, as well as in the development of new therapeutics for this condition.[6]

Sarcopenia, estimated by SMI, has proven to be an independent risk factor for the development of ACLF and mortality in WL, independent of kidney function or the grade of liver disease. These results would also support the evaluation of sarcopenia and highlight the importance of strategies aimed at improving sarcopenia in order to improve clinical outcomes in both the WL and post-LT settings.[3,42,43] Although the quantification of muscle mass by SMI is the gold standard, the costs and the high ionizing radiation exposure makes whole-body CT scan unsuitable for longitudinal assessments.[6] Not less importantly, the routine uses of the SGA, BIA, DXA, muscle strength, or physical performance have proven not to be a useful surrogate

TABLE 3 Mortality to last follow-up on the WL

Characteristics at Inclusion on the WL	Alive, n = 169 Count (%)/Median (IQR)	Death, n = 46 Count (%)/Median (IQR)	p	sHR (95% CI), in Multivariable Analysis	p in Multivariable Analysis
Age (years)	58 (50–64)	60 (54–65)	0.273		
Gender					
Female	71 (42)	11 (23.9)	**0.027**		
BMI	28 (25–32)	27 (24–32)	0.472		
Etiology			0.190		
HCV	36 (21.7)	13 (28.3)			
HBV	3 (1.8)	1 (2.2)			
Alcohol	36 (21.3)	12 (26.1)			
NASH	40 (23.7)	4 (8.7)			
Primary biliary cholangitis	9 (5.3)	1 (2.2)			
Primary sclerosing cholangitis	6 (3.6)	0 (0)			
Autoimmune hepatitis	11 (6.5)	3 (6.5)			
Others	8 (16.6)	12 (26.1)			
LT indication			0.244		
Decompensated cirrhosis	141 (83.4)	42 (91.3)			
Compensated cirrhosis with HCC	28 (16.6)	4 (8.7)			
HCC	45 (26.6)	13 (28.3)	0.852		
Diabetes	66 (39.1)	15 (32.6)	0.494		
Arterial hypertension	48 (28.4)	14 (30.4)	0.855		
History of ascites	115 (68)	42 (91.3)	**0.001**		
Refractory ascites	21 (18.3)	13 (31)	0.124		
History of encephalopathy	82 (48.5)	33 (71.7)	**0.007**		
History of variceal bleeding	39 (23.1)	9 (19.6)	0.693		
History of spontaneous infections	25 (14.8)	13 (28.3)	**0.048**		
Leukocytes (10^9/L)	4100 (3,000–5,400)	4,599 (3,004–5,836)	0.477		
Platelets (10^9/L)	84.1 (56.7–113.3)	79.95 (58.5–113.4)	0.688		
AST (IU/L)	44 (32–70)	43.5 (33–66)	0.812		
ALT (IU/L)	32 (22–60)	27 (19–47)	0.169		
ALP (IU/L)	122 (91–178)	127 (104–161)	0.826		
Bilirubin (mg/dL)	1.78 (1.18–3.5)	1.9 (1.44–3.2)	0.397		
Albumin (g/dL)	2.9 (2.6–3.32)	2.59 (2.35–2.8)	**<0.001**		
INR	1.56 (1.36–1.82)	1.66 (1.49–1.87)	0.085		
Creatinine (mg/dL)	0.78 (0.59–0.93)	0.88 (0.76–1.43)	**0.001**		
CysC (mg/L)	1.28 (1.05–1.66)	1.83 (1.55–2.44)	**<0.001**		
Creatinine/CysC	0.58 (0.48–0.71)	0.51 (0.42–0.65)	**0.030**		
Na (mmol/L)	136 (134–139)	134.5 (131–137)	**0.009**		
AKI	15 (12.1)	4 (13.8)	0.760		
CKD	3 (1.8)	7 (15.2)	**0.001**		
Child Pugh			**0.004**		
A	30 (17.8)	0 (0)			
B	78 (46.2)	21 (45.7)			
C	61 (36.1)	25 (54.3)			

TABLE 3 (Continued)

Characteristics at Inclusion on the WL	Alive, n = 169 Count (%)/Median (IQR)	Death, n = 46 Count (%)/Median (IQR)	p	sHR (95% CI), in Multivariable Analysis	p in Multivariable Analysis
Child Pugh in number	9 (7–10)	10 (9–11)	**0.004**		
MELD-Na	16 (12–20)	19 (16–24)	**<0.001**	**1.06 (1.01–1.11)**	**0.012**
Sarcopenia by SMI, cm^2/m^2	48 (42–56)	42 (38–48)	**0.003**		
Sarcopenia by SMI and gender (women < 39 cm^2/m^2 and men < 50 cm^2/m^2)	57 (33.7)	36 (78.3)	**<0.001**		
Sarcopenia HIBA score	−0.61 (−1.87 to 0.71)	0.63 (−1.02 to 1.31)	**0.003**	**1.21 (1.01–1.45)**	**0.047**

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; and NASH, nonalcoholic steatohepatitis.

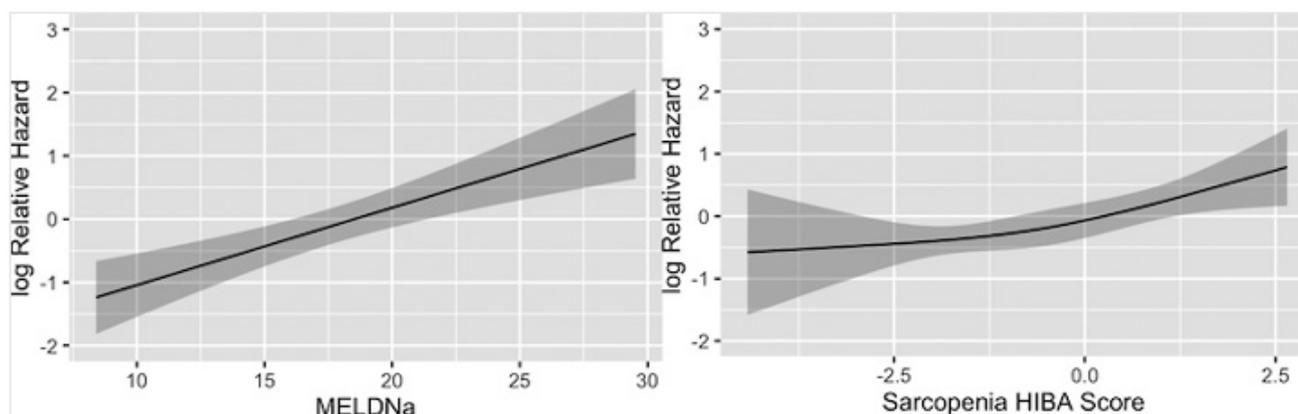They explain the p values that were significant, and the multivariate variables.

FIGURE 5 Association of MELD-Na and Sarcopenia HIBA Score with the (log) hazard of death on the WL for LT

measurement, requiring new tools.[41,42] In this direction, Tandon et al. developed a model based on the use of ultrasound and thigh muscle thickness, the advantage of which could be in safety, lower cost, and less radiation exposure, but its reproducibility is unknown, and studies in decompensated patients are required.[34]

This is the first study that evaluates the ratio creatinine/CysC in the prediction of sarcopenia by SMI in patients listed for LT. The use of these biomarkers and the set of other relevant variables (sex, BMI, and Child-Pugh) let the score also present an independent value in the prediction of mortality on the WL. The recognition of this condition following admission to WL is of vital importance in order to establish early therapeutic actions. In that direction, different approach strategies have recently been reported, such as physical activity,[44] reduction of fasting time,[45] adequate dietary assessment,[8] use of branched chain amino acids,[43] or even use of testosterone.[46]

Our study has limitations, particularly related to its single-center observational design, and our results will need to be validated in other cohorts of patients listed for LT in other geographical settings

and with different dynamics of the LT WL. However, we performed a bootstrapping internal validation and correction for optimism, which is more efficient than a split sample validation. In addition, CT scans were performed per clinical indication, so a selection bias cannot be excluded. Nevertheless, it must be stressed that only 12% of WL patients were excluded for absence of CT scanning. In addition, the granularity of the information and the standardization of the follow-up in our center minimize the impact of such limitations, and our results are consistent with the predictive value of sarcopenia in other populations of patients with cirrhosis. Another limitation of our study is the lack of a reference method for the determination of CysC, as well as the possible questioning of the gender cutoff values used for the definition of sarcopenia.[47,48] Similarly, the use of CysC as a biomarker is not routinely available in clinical practice, which may impact the applicability of our score on a daily basis. Finally, it is important to address a possible limitation: the capacity of the BMI in the setting of advanced liver disease and fluid overload in the risk of underestimating the presence of sarcopenia.

At this point, it is important to highlight that the model includes the Child-Pugh score, which considers the presence of ascites and could in some way capture the impact of fluid overload not contemplated in the BMI. In the same direction, the use of BMI or BMI dry weight presented a similar performance for the presence of sarcopenia (Supporting Table S2), and the use of standard BMI was the variable with the highest predictive weight within the model (Supporting Figure S2). In summary, in light of these results, we decided to simplify and use the standard BMI without adjusting for the presence of fluid overload.

To conclude, Sarcopenia HIBA score is an easy-to-use, reliable, reproducible, objective tool with excellent discriminatory capacity, which can help to properly evaluate the presence of sarcopenia, as well as monitor the evolution objectively. Moreover, higher values of the score are independently associated with mortality in WL. The evaluation of this risk factor through Sarcopenia HIBA score can improve the prognostic evaluation of patients on the WL for LT and allow us to identify a group of patients at risk of death while awaiting LT.

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 October 30, 2000, on the Protection of Personal Data in Argentina. All of the study data were treated anonymously with restricted access by only authorized personnel for the purposes of the study. The Institutional Review Board of the Hospital Italiano Buenos Aires approved the study (protocol number 3636).

CONFLICT OF INTEREST
A. Gadano is speaker for Bristol Myer Squibb, Gador, Gilead, Novartis, and Abbvie. He received educational grants from Gilead, Bristol Myers Squibb and Gador, and research grants from Gilead and Bristol Myers Squibb.

ORCID
Ezequiel Mauro https://orcid.org/0000-0002-0757-7676
Gonzalo Crespo https://orcid.org/0000-0002-1178-4897
Juan G. Abraldes https://orcid.org/0000-0003-3421-937X

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