A Prognostic Model of Acute-On-Chronic Liver Failure Based On Sarcopenia

Hong Peng

Guizhou Provincial People's Hospital

Qian Zhang

Guizhou Provincial People's Hospital

Siyi Lei

Guizhou Provincial People's Hospital

Tingting Xiong

Guizhou Provincial People's Hospital

Li Long

Guizhou Provincial People's Hospital

Yan Xiong

Guizhou Provincial People's Hospital

Liulu Zhang

Guizhou Provincial People's Hospital

Jinding Zheng

Guizhou Provincial People's Hospital

Xinhua Luo (✉ Luoxinhua1972@126.com)

Guizhou Provincial People's Hospital

Research Article

Keywords: Acute-on-chronic liver failure, Predictive model, Nutritional status, Sarcopenia, Liver transplantation, Survival, Progression

Posted Date: December 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1151335/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

Acute-on-chronic liver failure (ACLF) is characterized by the development of a syndrome associated with a high risk of short-term death in patients with acute decompensated cirrhosis, and better biomarkers are needed to predict such outcomes. Sarcopenia, a common complication of cirrhosis, is tightly associated with poor prognosis and increased mortality. In this study, the skeletal muscle index of ACLF patients was measured to determine whether sarcopenia combined with clinical parameters helps in identifying those at high risk of progression.

Methods

A total of 314 hospitalized ACLF patients were included and allocated into groups of transplantation-free survival ($n = 214$) or progression ($n = 100$) within 90 days. Muscle mass was assessed based on the skeletal muscle index. The optimal cutoff value of the AMPAS1 model (age, MELD score, platelet count, alpha-fetoprotein level, sarcopenia and more than one complication combination) for progressive prediction was identified using receiver operating characteristic (ROC) analysis.

Results

Sarcopenia was an independent risk factor for progression in the ACLF population (HR 3.705 95%CI 2.131-6.441, $P < 0.001$). AMPAS1 was a good predictor, with an area under the ROC curve of 0.908, and the cutoff value for poor outcome prediction was 0.21 (sensitivity 93.2%, specificity 71.1%).

Conclusion

We demonstrate that sarcopenia is a simple and objective biomarker for predicting short-term prognosis in patients with ACLF. Moreover, compared to conventional prognostic scores, AMPAS1 is a better model to predict 90-day adverse outcomes in ACLF patients.

Introduction

Acute-on-chronic liver failure (ACLF) involves rapid deterioration of liver function in chronic liver disease and is often associated with the development of serious complications such as hepatorenal syndrome and hepatic encephalopathy (HE) within a short period of time.(1, 2) ACLF has a high rate of short-term mortality, with 28- and 90-day mortality rates as high as 25% and 40%, respectively.(3) Liver transplantation may be the only curative treatment for these patients. Although prognostic scores including Model for End-stage Liver Disease [MELD] and MELD-Na scores help guide donor liver allocation for transplantation, both of these scoring systems lack important parameters that reflect the

nutritional and functional status of patients with ACLF. Indeed, the MELD score did not capture ACLF severity among candidates listed for liver transplant (LT) in a large cohort study.(4) Another multicenter study of 18,979 patients with ACLF in the United States found that MELD-Na did not capture 90-day mortality risk in ACLF, with only a small proportion of ACLF patients exceeding the median MELD thresholds for transplantation in designated LT centers.(5)

To help clinicians predict the condition of patients and take timely intervention measures, a clinical index closely related to the prognosis of ACLF patients and a better prediction model are needed. Sarcopenia, a common complication of cirrhosis, is defined as a progressive and generalized loss of skeletal muscle mass, strength, and function. A recent study found that sarcopenia is strongly and independently associated with a high risk of mortality in patients with cirrhosis.(6) However, there are few real-world studies of sarcopenia in predicting the prognosis of ACLF. Therefore, in this study, a new model was developed to predict 90-day progressive risk in patients with ACLF by measuring the L3 skeletal muscle index in combination with other key clinical indicators.

Methods

Patients

For this retrospective study, we recruited all patients with ACLF (defined as TBIL ≥ 171 $\mu\text{mol/L}$ and INR ≥ 1.5 according to the Chinese criteria(7)) treated at our institution between July 2019 and March 2021. We excluded patients younger than 18 years old, those who were pregnant, and those diagnosed with hepatocellular carcinoma or any extrahepatic malignancy, as well as patients with comorbidities associated with poor outcomes (severe cardiopulmonary disease defined by a New York Heart Association score > 3 , oxygen/steroid-dependent chronic obstructive pulmonary disease, chronic kidney disease). All patients were given standard medical treatments, including artificial liver support systems, energy supplements, intravenous infusion of albumin and plasma, and preventive treatment for complications after admission. The 90-day transplantation-free survival rate was determined.

The present study was approved by the ethics committee of Guizhou Provincial People's Hospital and performed according to the ethical guidelines of the 1975 Declaration of Helsinki. The requirement for obtaining informed consent from patients was waived because of the retrospective nature of the study.

Data collection

Demographic data and laboratory parameters for all patients were extracted through retrospective review of medical records. Laboratory parameters included prealbumin, albumin, alanine aminotransferase, aspartate aminotransferase, creatinine, TBIL, INR, white blood cell count, platelet count, and blood urea nitrogen. Effective hepatic blood flow (EHBF) was measured by the indocyanine green (ICG) clearance test. Prognostic scores (including Model for End-stage Liver Disease [MELD] and MELD-Na scores) were calculated using baseline values of relevant parameters (measured at the time of admission).

Evaluation of skeletal muscle mass and definition of sarcopenia

Skeletal muscle mass was evaluated according to the skeletal muscle index (SMI) based on computer tomography (CT) scans at L3.(8) SMI was calculated by normalizing the L3 skeletal muscle areas by the square of the patient's height (m^2). (9) The muscle masses evaluated in the L3 region were the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. Skeletal muscle is identified and quantified by Hounsfield unit (HU) thresholds of -29 to $+150$ (10); with these specific HU thresholds, SMI measurements are not influenced by the presence of ascites. This analysis was performed using the diagnostic software ImageJ (NIH, Bethesda, MD, USA). (11) Sarcopenia was defined according to the Japan Society of Hepatology guidelines for sarcopenia in liver disease as $\text{L3 SMI} < 38 \text{ cm}^2/\text{m}^2$ for female patients and $< 42 \text{ cm}^2/\text{m}^2$ for male patients.(12)

Statistical analysis

Continuous variables were analyzed using Student's t test or the Mann–Whitney U test, as appropriate; the results are expressed as the mean $\pm$ standard deviation or median (25th centile; 75th centile). Categorical data were compared using the χ^2 test, and the results are expressed as numbers (percentages). Cox proportional hazard model and receiver operating characteristic curve (ROC) analyses were used to identify independent factors for progression in patients with ACLF. Finally, the independent predictors obtained from the above screening progress were considered for nomogram construction. Calibration curves and the C-index were subsequently evaluated to assess the calibration of the model. Cumulative rates of the 90-day transplantation-free survival rate were plotted using a Kaplan–Meier curve and compared using the log-rank test. All statistical analyses were carried out using SPSS 25.0 (Chicago, IL, USA) and R 3.6.0. Statistical significance was set at two-sided $P < 0.05$.

Results

Patient characteristics

Of 392 patients who were recruited for the present study, 78 were excluded: 42 due to hepatocellular carcinoma, 12 due to other extrahepatic malignancies, 5 due to pregnancy, 4 due to severe cardiopulmonary disease, 3 due to chronic obstructive pulmonary disease, and 12 due to chronic kidney disease. Ultimately, 314 patients with ACLF were enrolled for analysis. The baseline characteristics and biochemical data of the participants are listed in Table 1. Among the 314 participants, 214 were in the transplantation-free survival group, and 100 were in the progression group (76 died; 24 underwent liver transplantation), representing a 90-day transplantation-free survival rate of 68.2%. Overall, mean age, MELD score, lymphocyte count, NLR, TBIL, INR, CRP, IL-6, proportion of sarcopenia and more than one complication were higher in the patients who experienced progression; conversely, the mean L3 SMI, platelet count, ALT, sodium and AFP were lower ($P < 0.05$). At the same time, we compared 28-day transplantation-free survival in the 314 patients, with 272 (86.6%) having transplantation-free survival.

MELD score, TBIL, INR and proportion of more than one complication were higher in the progression group, and age and CRP were close to statistically significant (Table S1).

Table 1
Baseline characteristics of the study participants

Characteristic	Total (N = 314)	90-day transplantation-free survival (n=214)	Progression (n=100)	<i>p</i> value
Age, y	47.0 (34.8-54.3)	44.0 (34.5-53.0)	49.0 (37.5-64.0)	0.006
Sex, n (%)				
Male	246 (78.30)	169 (79.3)	77 (76.20)	
Female	68 (21.70)	44 (20.7)	24 (23.80)	
MELD score	22.0 (16.8-25.0)	22.0 (16.0-25.0)	22.0 (18.0-29.0)	<0.001
Etiology, n (%)				0.484
HBV/HCV	177 (56.40)	118 (55.40)	59 (58.40)	
Alcohol	65 (20.70)	49 (23.00)	16 (15.80)	
HBV/HCV+Alcohol	24 (7.60)	16 (7.50)	8 (7.90)	
Others	48 (15.30)	30 (14.10)	18 (17.80)	
L3 SMI, cm ² /m ²	40 (36-45.5)	42.6 (38.0-47.0)	37.0 (30.0-40.0)	<0.001
Sarcopenia, n (%)	154 (49.0)	79 (36.9)	75 (75)	<0.001
BMI	23.7 (21.6-26.4)	23.7 (21.5-29.5)	25.0 (22.1-26.5)	0.989
Platelet (×10 ⁹ /L)	88.5 (60.8-131.0)	98 (64.0-150.0)	59 (43.5-92.0)	<0.001
Neutrophil (×10 ⁹ /L)	2.95 (1.26-5.44)	3.39 (1.35-6.10)	1.30 (0.74-4.24)	0.435
Lymphocyte (×10 ⁹ /L)	1.45 (0.85-4.02)	1.41 (0.94-4.39)	1.68 (0.76-3.91)	0.016
NLR	2.21 (0.26-6.03)	2.23 (0.37-6.17)	0.40 (0.16-6.64)	0.019

Continuous variables are expressed as the median (IQR).

Abbreviations: MELD score, end-stage liver disease score; HBV, hepatitis B virus; HCV, hepatitis C virus; L3 SMI, L3 skeletal muscle index; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

*More than one complication included gastroesophageal varices, hepatic encephalopathy, hepatorenal syndrome and infections.

Characteristic	Total (N = 314)	90-day transplantation-free survival (n=214)	Progression (n=100)	<i>p</i> value
PLR	57.88 (17.40-101.52)	61.84 (24.20-101.61)	20.68 (12.09-84.34)	0.955
Serum albumin, g/L	28.1 (25.8-31.3)	28.5 (26.8-33.1)	27.1 (20.6-29.0)	0.31
Creatinine, μ mol/L	71.0 (60.0-88.0)	68.9 (56.1-81.5)	87.7 (65.5-128.1)	0.068
Total bilirubin, μ mol/L	244.6 (161.7-332.5)	222.4 (150.6-328.0)	264.6 (220.2-459.9)	<0.001
Alanine aminotransferase, U/L	112.5 (36.5-522.3)	129.0 (40.5-532.5)	62.0 (28.5-151.0)	0.033
International normalized ratio	1.82 (1.56-2.09)	1.78 (1.56-2.04)	1.91 (1.63-2.60)	<0.001
C-reactive protein, mg/L	12.06 (7.27-28.25)	11.00 (6.92-22.25)	25.13 (10.60-48.69)	0.002
Interleukin-6, pg/mL	18.34 (8.55-32.46)	16.56 (7.50-23.11)	44.98 (18.29-61.93)	0.002
Effective hepatic blood flow, L/min	0.20 (0.14-0.27)	0.21 (0.16-0.28)	0.17 (0.11-0.24)	0.063
Sodium, mmol/L	136.0 (133.0-138.4)	136.7 (133.5-138.7)	134.0 (131.7-138.3)	0.009
Prealbumin, g/L	59.9 (50-89.2)	57.3 (50-87.0)	72.8 (50-94.05)	0.806
Alpha-fetoprotein, mmol/L	28.0 (5.0-119.6)	39.2 (6.0-125.4)	15.0 (4.1-85.9)	0.006
*More than one complication, n (%)	168(53.5)	85 (39.9)	83(82.2)	<0.001
Continuous variables are expressed as the median (IQR).				
Abbreviations: MELD score, end-stage liver disease score; HBV, hepatitis B virus; HCV, hepatitis C virus; L3 SMI, L3 skeletal muscle index; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.				
*More than one complication included gastroesophageal varices, hepatic encephalopathy, hepatorenal syndrome and infections.				

Factors Associated With Progression

Univariate analysis revealed sarcopenia, more than one complication (including gastroesophageal varices, hepatic encephalopathy, hepatorenal syndrome and infection), age, MELD score, $\text{CRP} \geq 20 \text{ mg/L}$, $\text{EHBF} < 0.53 \text{ L/min}$, $\text{sodium} < 135 \text{ mmol/L}$, $\text{platelet} < 100 \times 10^9/\text{L}$, $\text{NLR} \geq 2.8$, and $\text{AFP} < 5 \text{ mmol/L}$ to be associated with 90-day progression in patients with ACLF (cutoff values of CRP, EHBF, platelet, NLR and AFP were analyzed by ROC curve analysis). However, multivariate analysis identified only sarcopenia, more than one complication, age, MELD score, $\text{platelet} < 100 \times 10^9/\text{L}$ and $\text{AFP} < 5 \text{ mmol/L}$ as independent predictors of progression (Table 2). In addition, the C-index of internal validation was 0.815, which indicated that the model had a high degree of differentiation and accuracy. We also compared independent risk factors in patients with progression at 28 days, but only age, MELD score and CRP were found to be independent predictors by multivariate analysis (Table S2).

Table 2
Univariate and multivariate Cox proportional hazard models to predict 90-day progression in ACLF patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	P value
Age	1.4	1.047-1.872	0.023	1.505	1.026-2.208	0.036
MELD score	2.103	1.348-3.281	0.001	1.886	1.127-3.154	0.016
C-reactive protein $\geq$ 20 mg/L	2.013	1.337-3.031	0.001			
Effective hepatic blood flow <0.53 L/min	3.179	1.146-8.818	0.026			
Sodium <135 mmol/L	1.732	1.167-2.569	0.006			
Platelet $<100 \times 10^9$ /L	1.750	1.152-2.659	0.009	2.658	1.319-5.357	0.006
NLR ≥ 2.8	2.241	1.485-3.382	<0.001			
Alpha-fetoprotein <5 mmol/L	1.856	1.217-2.832	0.004	1.955	1.160-3.294	0.012
Sarcopenia	3.705	2.131-6.441	<0.001	3.299	1.786-6.096	<0.001
*More than one complication	4.943	2.965-8.239	<0.001	3.246	1.600-6.587	0.001
Abbreviations: HR, hazard ratio; CI, confidence interval; MELD score, end-stage liver disease score; NLR, neutrophil-to-lymphocyte ratio.						
*More than one complication included gastroesophageal varices, hepatic encephalopathy, hepatorenal syndrome and infections.						

Analysis Of The Predictive Value Of The Model

Next, we built a nomogram by combining prognostic factors, including age, MELD score, platelet count, AFP, sarcopenia, and more than one complication (Fig. 1A), and the vertical line from the coordinate axis of each risk index was used to obtain corresponding scores. These scores were added to obtain the total score, corresponding to the 90-day transplantation-free survival rate in the last coordinate axis, and the survival percentage for each individual was obtained. To assess our model, we drew a calibration curve

based on the actual incidence and the prediction rate, which showed that the apparent curve had a similar prediction function compared with the ideal model (Fig. 1B).

Furthermore, the prognostic value of the MELD score and MELD-Na score for predicting outcomes was assessed by analyzing the area under the ROC curve. The sensitivity and specificity were 50.0% and 77.5% for the MELD score and 78.0% and 49.0% for the MELD-Na score, respectively. The powers of the MELD score and MELD-Na score for predicting outcome were not significantly different, as indicated by their similar area under curve values (0.691 and 0.687, respectively, $P = 0.850$). When age, MELD score, platelet count, AFP, sarcopenia and more than one complication were combined (AMPAS1), the area under the curve for predicting mortality was 0.908, which was higher than that of either parameter alone (both $P < 0.05$), and the cutoff value, sensitivity, and specificity were 0.21, 93.2%, 71.1% (Fig. 2).

Two Risk Groups For Prediction Of 90-day Progression

Finally, patients were divided into 2 significantly different risk groups (high and low) according to the preselected cutoff points, and 90-day progression in these patients was compared. According to previous clinical studies, patients with MELD scores > 20 and MELD-Na scores ≥ 25 are considered to be at high risk,(13–15) and a total of 199 and 116 ACLF patients in our study met these criteria. In addition, the cutoff value of AMPAS1 was 0.21. In total, 89 high-risk patients were screened by ROC analysis; according to Cox proportional hazard regression, patients in the high-risk group with MELD scores > 20 had a 2.7-fold higher likelihood of progressive events than did patients in the low-risk group with MELD scores below 20, and those in the high-risk group with MELD-Na scores had a 2.5-fold higher likelihood of progression than did low-risk patients with MELD-Na scores below 25. Moreover, those with sarcopenia had a 3.7-fold higher likelihood of progression than did those without sarcopenia, and $AMPAS1 \geq 0.21$ in the high-risk group was associated with a 15.9-fold higher progressive event likelihood than low-risk patients with AMPAS1 below 0.21 (Table 3). Moreover, 90-day cumulative survival rates were compared using the different models between the low- and high-risk groups. Survival for patients with $AMPAS1 \geq 0.21$ was extremely low, at 39%; survival for those with sarcopenia, MELD-Na and MELD was 49.8%, 52.6% and 59.8%, respectively. Similarly, the median survival 61.3 days based on AMPAS1 (95%CI (55.3–67.5)), 66.8 days based on sarcopenia (95%CI (61.3–72.5)), 64.7 days based on MELD-Na (95%CI (59.1–70.5)) and 69 days based on MELD (95%CI (65.0–73.2)). There was a significant difference in survival curves among the groups ($P < 0.001$) (Fig. 3).

Table 3
Risk of 90-day progressive events for 2 risk groups defined by test-specific cutoffs.

Risk groups	Event (%)	Hazard ration	<i>p</i> value
MELD score			
≤ 20	20 (17.54)	1	-
> 20	80 (40.20)	2.701 (1.655-4.412)	<0.001
MELD-Na score			
<25	45 (22.73)	1	-
≥ 25	55 (47.41)	2.529 (1.705-3.753)	<0.001
Sarcopenia			
No	23 (16.67)	1	-
Yes	77 (50.00)	3.705 (2.131-6.441)	<0.001
AMPAS1			
<0.21	10 (5.49)	1	-
≥ 0.21	90 (60.67)	15.945 (6.364-39.953)	<0.001
Hazard ratios from univariable Cox proportional hazard regression for prediction of 90-day progressive events according to low- and high-risk patients, with P values for between-group differences shown as hazard ratios. We used previously published cutoff points to define the risk groups.			
Abbreviations: MELD score, End-stage Liver Disease score; MELD-Na, End-stage Liver Disease includes serum sodium score; AMPAS1, including age, MELD score, platelet, AFP, sarcopenia and more than one complication.			

Discussion

Differences between Eastern and Western diagnostic criteria for ACLF have resulted in considerable discrepancies in the identification, rescue regimen, and eventual prognosis of the condition.(16–18) The main causes of liver failure in Western countries are nonsteroidal anti-inflammatory drugs and alcohol; in China, the main cause is hepatitis virus infection, especially hepatitis B virus.(19) The established MELD score and MELD-Na score prognostic models are based on European and American studies, and better predictive models for Asian patients with ACLF need to be further explored. For the present study, we used Chinese criteria for ACLF, which have been validated for the diagnosis of ACLF in China. Our analyses of a cohort of patients with ACLF revealed three major findings. First, to our knowledge, this is the first study to report sarcopenia as an independent risk factor for progression in an ACLF population. Second, we are the first to combine sarcopenia with clinical indicators to predict poor 90-day outcomes in patients with ACLF. Third, MELD scores and MELD-Na scores did not capture the severity of 90-day adverse outcomes

in patients with ACLF, whereas our new model, AMPAS1, was a good predictor of such outcomes. Interestingly, by comparing clinical markers of patients with 28-day progression to those with 90-day progression, we also found that sarcopenia had no predictive value for 28-day progression. We suspect that the reason for this difference may be related to the different mechanisms of disease progression. Patients who experienced progression at 28 days were more likely to have an acute inflammatory storm with massive hepatocyte necrosis, whereas progression at 90 days may be associated with anabolism and even host immune function.

The MELD score is the most commonly used model to predict the prognosis of liver disease and incorporates three laboratory variables: TBIL, INR, and creatinine.(13, 14) Although the MELD score considers liver dysfunction and renal insufficiency, it does not incorporate other crucial factors, such as HE, organ failures, or infection, which can affect prognosis.(20) Moreover, our data show that both the MELD score and MELD-Na score do not fully capture underlying disease severity in ACLF. This is likely due to the effect of extrahepatic organ failures on patient outcomes, which are not considered when calculating MELD-Na. Scores other than MELD or MELD-Na based on organ failure may be more appropriate to predict prognosis in patients with ACLF. Previous studies have identified several factors, including age, AFP, and platelets, to be associated with poor outcomes of liver failure, consistent with our study.(7) In addition, the nutritional status of patients with liver disease is a problem that is easy to ignore. Sarcopenia has also been found to be associated with high mortality and poor posttransplant outcomes in patients awaiting liver transplantation.(21–23) The present study complements these studies, adding sarcopenia, complications and clinical indicators as a predictor of prognosis in patients with ACLF, and combining these elements with the MELD score adds to the power of the score for predicting progression.

The relationship between sarcopenia and unfavorable outcomes of ACLF is complex and has yet to be fully elucidated. Because ACLF itself is associated with mortality, systemic inflammation, and organ failure, it is unclear which factors associated with sarcopenia are relevant for ACLF. The present study indicates that sarcopenia is an independent risk factor for progression in the ACLF population, as patients presenting sarcopenia had a higher risk of LT or mortality than those without sarcopenia. Our conclusions are consistent with those of Montano-Loza and colleagues,(24) who determined that sarcopenia is associated with a 5-fold increased risk of mortality in patients with cirrhosis, independent of the MELD-Na score. Tandon *et al*/ also reported that sarcopenia is associated with a 2-fold increased risk of liver transplant waitlist mortality.(25) Sarcopenia results from an imbalance between protein synthesis and catabolism. Major pathways involved in peripheral muscle breakdown include activation of autophagy and the ubiquitin–proteasome pathway (UPP) and the mammalian target of rapamycin (mTOR) pathway.(26, 27) Myostatin, a myokine, is an inhibitor of protein synthesis and regeneration. In addition, a number of proinflammatory cytokines (TNF- α , IL-6, IL-1 and IFN- γ) have been reported to trigger muscle wasting, but the precise contributions of these factors remain controversial and unclear under different conditions.(26) Hyperammonemia, which upregulates myostatin levels and activates autophagy, also plays a crucial role in the development of sarcopenia.(28) Elevated levels of ammonia lead to impairment of the mTOR pathway through increased mitochondrial dysfunction and production

of reactive oxygen species (ROS).(28) We hypothesize that an impaired liver-muscle axis is an essential contributor to ACLF. Consequently, malnutrition has been shown to lead to increased liver damage and worse outcomes.(29)

Our study also has some limitations. First, the study was retrospective in nature, and the sample size was small. Second, L3 SMI levels were not measured dynamically; thus, it remains unclear whether dynamic changes in L3 SMI levels have more clinical value in predicting adverse outcomes in patients with ACLF. Third, the mechanism underlying the contribution of sarcopenia to the progression of ACLF remains unknown. Further prospective multicenter studies are needed to clarify these uncertainties and confirm our conclusions.

In summary, the current study indicates that sarcopenia is a simple and objective biomarker able to predict 90-day prognosis in patients with ACLF. Nutritional status may provide valuable information to supplement conventional approaches of assessing disease condition in these patients, representing a useful tool in clinical practice to assess patient prognosis and help clinicians identify individuals in need of nutritional intervention. AMPAS1 is a better model to predict 90-day adverse outcomes in patients with ACLF than conventional prognostic scores.

Declarations

Author contribution Xinhua Luo conceived and designed the study. Hong Peng contributed significantly to analysis and manuscript preparation. Qian Zhang performed the data analysis and wrote the manuscript. Siyi Lei, Tingting Xiong, Li Long, Yan Xiong, Liulu Zhang, Jinding Zheng helped to perform the analysis with constructive discussions. All authors read and approved the manuscript.

Funding We received no funding/grant support for this study.

Availability of data and materials The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval This study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Guizhou Provincial People's Hospital.

Consent to participate Informed consent was waived because of the retrospective nature of the study.

References

1. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, et al. Acute-on chronic liver failure. *J Hepatol.* 2012;57(6):1336–48. doi: 10.1016/j.jhep.2012.06.026. PubMed PMID: 22750750.
2. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. *Gut.* 2017;66(3):541-53. doi: 10.1136/gutjnl-2016-312670. PubMed PMID: 28053053.

3. Hernaez R, Kramer JR, Liu Y, Tansel A, Natarajan Y, Hussain KB, et al. Prevalence and short-term mortality of acute-on-chronic liver failure: A national cohort study from the USA. *J Hepatol*. 2019;70(4):639–47. doi: 10.1016/j.jhep.2018.12.018. PubMed PMID: 30590100.
4. Abdallah MA, Kuo Y-F, Asrani S, Wong RJ, Ahmed A, Kwo P, et al. Validating a novel score based on interaction between ACLF grade and MELD score to predict waitlist mortality. *J Hepatol*. 2021;74(6):1355–61. doi: 10.1016/j.jhep.2020.12.003. PubMed PMID: 33326814.
5. Hernaez R, Liu Y, Kramer JR, Rana A, El-Serag HB, Kanwal F. Model for end-stage liver disease-sodium underestimates 90-day mortality risk in patients with acute-on-chronic liver failure. *J Hepatol*. 2020;73(6):1425–33. doi: 10.1016/j.jhep.2020.06.005. PubMed PMID: 32531416.
6. Tantai X, Liu Y, Yeo YH, Praktijnjo M, Mauro E, Hamaguchi Y, et al. Effect of sarcopenia on survival in patients with cirrhosis: A systematic review and meta-analysis. *J Hepatol*. 2021. doi: 10.1016/j.jhep.2021.11.006. PubMed PMID: 34785325.
7. [Guideline for diagnosis and treatment of liver failure]. *Zhonghua Gan Zang Bing Za Zhi*. 2019;27(1):18–26. doi: 10.3760/cma.j.issn.1007-3418.2019.01.006. PubMed PMID: 30685919.
8. Koya S, Kawaguchi T, Hashida R, Hirota K, Bekki M, Goto E, et al. Effects of in-hospital exercise on sarcopenia in hepatoma patients who underwent transcatheter arterial chemoembolization. *J Gastroenterol Hepatol*. 2019;34(3):580–8. doi: 10.1111/jgh.14538. PubMed PMID: 30402913.
9. Sinclair M, Gow PJ, Grossmann M, Angus PW. Review article: sarcopenia in cirrhosis—aetiology, implications and potential therapeutic interventions. *Aliment Pharmacol Ther*. 2016;43(7):765–77. doi: 10.1111/apt.13549. PubMed PMID: 26847265.
10. 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(1):115–22. PubMed PMID: 9655763.
11. Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods*. 2012;9(7):671–5. PubMed PMID: 22930834.
12. Nishikawa H, Shiraki M, Hiramatsu A, Moriya K, Hino K, Nishiguchi S. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): Recommendation from the working group for creation of sarcopenia assessment criteria. *Hepatol Res*. 2016;46(10):951–63. doi: 10.1111/hepr.12774. PubMed PMID: 27481650.
13. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). *Hepatology*. 2007;45(3):797–805. PubMed PMID: 17326206.
14. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33(2):464–70. PubMed PMID: 11172350.
15. Sundaram V, Jalan R, Wu T, Volk ML, Asrani SK, Klein AS, et al. Factors Associated with Survival of Patients With Severe Acute-On-Chronic Liver Failure Before and After Liver Transplantation. *Gastroenterology*. 2019;156(5). doi: 10.1053/j.gastro.2018.12.007. PubMed PMID: 30576643.

16. Selva Rajoo A, Lim S-G, Phyo WW, Tun T, Dan Y-Y, Lee Y-M, et al. Acute-on-chronic liver failure in a multi-ethnic Asian city: A comparison of patients identified by Asia-Pacific Association for the Study of the Liver and European Association for the Study of the Liver definitions. *World J Hepatol.* 2017;9(28):1133–40. doi: 10.4254/wjh.v9.i28.1133. PubMed PMID: 29075369.
17. Arroyo V, Moreau R, Jalan R, Ginès P. Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis. *J Hepatol.* 2015;62(1 Suppl):S131-S43. doi: 10.1016/j.jhep.2014.11.045. PubMed PMID: 25920082.
18. Li H, Xia Q, Zeng B, Li S-T, Liu H, Li Q, et al. Submassive hepatic necrosis distinguishes HBV-associated acute on chronic liver failure from cirrhotic patients with acute decompensation. *J Hepatol.* 2015;63(1):50–9. doi: 10.1016/j.jhep.2015.01.029. PubMed PMID: 25646889.
19. 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(4):453–71. doi: 10.1007/s12072-014-9580-2. PubMed PMID: 26202751.
20. Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. *Liver Transpl.* 2007;13(10):1366–71. PubMed PMID: 17520742.
21. van Vugt JLA, Levolger S, de Bruin RWF, van Rosmalen J, Metselaar HJ, Ijzermans JNM. Systematic Review and Meta-Analysis of the Impact of Computed Tomography-Assessed Skeletal Muscle Mass on Outcome in Patients Awaiting or Undergoing Liver Transplantation. *Am J Transplant.* 2016;16(8):2277–92. doi: 10.1111/ajt.13732. PubMed PMID: 26813115.
22. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg.* 2010;211(2):271–8. doi: 10.1016/j.jamcollsurg.2010.03.039. PubMed PMID: 20670867.
23. Kaido T, Ogawa K, Fujimoto Y, Ogura Y, Hata K, Ito T, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. *Am J Transplant.* 2013;13(6):1549–56. doi: 10.1111/ajt.12221. PubMed PMID: 23601159.
24. Montano-Loza AJ. Clinical relevance of sarcopenia in patients with cirrhosis. *World J Gastroenterol.* 2014;20(25):8061-71. doi: 10.3748/wjg.v20.i25.8061. PubMed PMID: 25009378.
25. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. *Liver Transpl.* 2012;18(10):1209–16. doi: 10.1002/lt.23495. PubMed PMID: 22740290.
26. Han HQ, Zhou X, Mitch WE, Goldberg AL. Myostatin/activin pathway antagonism: molecular basis and therapeutic potential. *Int J Biochem Cell Biol.* 2013;45(10):2333–47. doi: 10.1016/j.biocel.2013.05.019. PubMed PMID: 23721881.
27. Dreyer HC, Drummond MJ, Pennings B, Fujita S, Glynn EL, Chinkes DL, et al. Leucine-enriched essential amino acid and carbohydrate ingestion following resistance exercise enhances mTOR

- signaling and protein synthesis in human muscle. *Am J Physiol Endocrinol Metab*. 2008;294(2):E392-E400. PubMed PMID: 18056791.
28. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol*. 2016;65(6):1232–44. doi: 10.1016/j.jhep.2016.07.040. PubMed PMID: 27515775.
29. Lai JC, Rahimi RS, Verna EC, Kappus MR, Dunn MA, McAdams-DeMarco M, et al. Frailty Associated With Waitlist Mortality Independent of Ascites and Hepatic Encephalopathy in a Multicenter Study. *Gastroenterology*. 2019;156(6):1675–82. doi: 10.1053/j.gastro.2019.01.028. PubMed PMID: 30668935.

Figures

A

B

Figure 1

Nomogram to predict the probability of 90-day transplantation-free survival in patients with acute-on-chronic liver failure. And Calibration curve to predict the probability of 90-day transplantation-free survival.

Figure 2

Receiver operating characteristic curves indicating the relative efficiencies of the Chinese cohort with acute-on-chronic liver failure of end-stage liver disease (MELD) score. End-stage liver disease includes serum sodium (MELD-Na) and the combination of age, MELD score, platelet count, AFP, sarcopenia and more than one complication (AMPAS1) for predicting 90-day progression in patients with acute-on-chronic liver failure.

Figure 3

Kaplan–Meier curve depicting 90-day transplantation-free survival in patients with acute-on-chronic liver failure.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementarymaterial.docx](#)