Sarcopenia should be evaluated in patients with acute-on-chronic liver failure and candidates to liver transplantation.

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awareness regarding HCC surveillance regardless of the method of surveillance.

Finally, we echo the authors' concerns regarding potential tissue accumulation and adverse effects of gadolinium if contrast-enhanced AMRI is used for HCC screening. Not only this, contrast-enhanced AMRI is associated with greater acquisition time and cost and may hamper patient compliance. Thus, we assert that for AMRI to be safe and acceptable, non-contrast rather than contrast-enhanced AMRI should be utilized.

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Sarcopenia should be evaluated in patients with acute-on-chronic liver failure and candidates for liver transplantation

To the Editor:

We have read with great interest the manuscript of Belli *et al.*[1] reporting a wide variation in listing for patients with acute-on-chronic liver failure (ACLF) in Europe despite favorable outcome after liver transplantation (LT). The authors have particularly observed, after multivariate analyses, the negative impact of pre-LT multi drug resistant organism (MDRO) infection, arterial lactate levels at LT >4 mmol/L and the need for renal replacement therapy (RRT) at LT.[1] Identifying risk factors associated with poorer post-LT outcomes in this population is crucial and the authors must be congratulated for their efforts in this regard. However, the retrospective design of this study and others in the field might bias the analyses, as several variables, considered as important, have not been studied yet. Indeed, as highlighted by the authors in the discussion section, the impact of sarcopenia on post-LT outcome was not assessed in this study nor in others in the field. As only few retrospective studies are available on this topic, it is unclear if clinicians considered the nutritional status of patients with ACLF at time of deciding on transplantability. In a new analysis of our cohort previously published in *Journal of Hepatology*[2] reporting favorable and non-different 1-year survival in patients transplanted with ACLF grade 3 compared to matched control patients transplanted with ACLF grade <3 or no ACLF, we aimed to assess if radiological parameters of sarcopenia were associated with outcome. All patients included in our first publication were considered in the present study. Radiological parameters of sarcopenia were

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retrospectively assessed on CT scans performed at time of LT (±15 days) when available using transversal right psoas muscle thickness at the umbilical level/height (TPMT/height in mm/m)[3] and psoas muscle index (PMI in cm^2/m^2) at the L3-L4 level.[4] Age, hospitalization status (home, general ward, intensive care unit [ICU]), model for end-stage liver disease score and grade of ACLF were available for patients at time of LT. We studied the main patient characteristics in the ACLF cohort that were associated with 1-year survival on univariate and multivariate analysis using the Cox proportional hazards regression models. The overall survival curves at 1 year were estimated using the Kaplan-Meier method and were compared using the log-rank test. Statistical testing was done at the 2-tailed α level of 0.05. CT scans allowing for the assessment of TPMT/height and PMI were available in 584 out of 629 patients (93%) initially included in our previous study: 270/292 patients without ACLF, 105/119 patients with ACLF grade 1, 139/145 ACLF grade 2 and 70/73 ACLF grade 3. For these patients, 1-year survival was respectively 91% (95% CI 87-94) *vs.* 83% (76-90) *vs.* 88% (83-94) *vs.* 83% (74-92), p = 0.1. TPMT/height was 18.4 mm/m (15.4-21.1) *vs.* 17.5 mm/m (15.4 - 20.0) *vs.* 16.9 mm/m (14.6-20.2) *vs.* 16.1 mm/m (14.1-18.6), respectively, p <0.0001. PMI was 6.9 cm^2/m^2 (5.6-8.3) *vs.* 6.3 cm^2/m^2 (5.1-7.3) *vs.* 6.1 cm^2/m^2 (5.2-7.4) *vs.* 5.4 cm^2/m^2 (4.6-6.5), respectively, p <0.0001. Uni and multivariate analyses associated with 1-year survival in the ACLF cohort are provided in Table 1 and suggest an independent association between 1-year mortality and radiological parameters of sarcopenia. In a second step, we aimed to assess the ability of the already published thresholds of TPMT/height (16.6 mm/m)[3] and PMI (5.1 cm^2/m^2 in men and 4.3 cm^2/m^2) in women[4] to identify patients with ACLF with poorer outcome following LT. These thresholds respectively identified 2 populations with different 1-year survival: 91% (86-96) *vs.* 79% (73-86), p = 0.004 (Fig. 1A) and 88% (84-92) *vs.* 75% (65-85), p = 0.007 (Fig. 1B).

In sensitivity analyses according to sex, there was only a trend towards an association of these parameters with 1-year survival in men while the association was independent in women, in cox regression analyses (Table 1). In the same line, women with low TPMT/height and PMI according to established thresholds experienced lower survival 77% (67-88) *vs.* 97% (91-100), p = 0.01, and 74% (56-90) *vs.* 88% (81-96), p = 0.04, respectively. Men with low PMI had significant lower 1-year survival (76% (63-88) *vs.* 88% (83-93), p = 0.05). Male patients with low TPMT/height experienced a trend towards lower survival (80% (73-85) *vs.* 89% (84-95), p = 0.07).

The present analyses on our previously published cohort suggest three important considerations. First, even if non-different 1-year survivals after LT were observed, patients transplanted with ACLF showed significantly decreased muscle mass compared to patients without ACLF, with the most severe sarcopenia observed in ACLF grade 3 patients. This suggests that despite a stringent selection process, only about 3% of patients with cirrhosis in the ICU were selected for LT,[2] some patients with severe sarcopenia were still carefully chosen for LT. Second, and despite the first observation, patients with the most severe sarcopenia have the lowest 1-year survival independently of other cofounding factors. Third, the evaluation of sarcopenia by psoas measurements seems less sensitive in men than in women, for transplanted patients with ACLF. However, due to the intrinsic retrospective design of our analyses, patients with the most severe sarcopenia still had acceptable outcomes.

Nonetheless, our study has several limitations mainly related to the use of psoas-related sarcopenia parameters (variation of

Table 1. Multivariate analysis of factors associated with 1-year mortality in patients with ACLF at time of liver transplantation.

	Univariate analysis			Multivariate analysis		
Covariant	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Male sex	1.11	0.56 -1.98	0.86			
Age (per 10-year increase)	0.92	0.72-1.34	0.92			
MELD score	1.01	0.96-1.06	0.83			
Hospitalization status	1.51	0.98-2.35	0.06	1.43	0.91-2.22	0.11
Grade ACLF	0.91	0.64-1.43	0.84			
TPMT/height	0.92	0.86-0.99	0.05	0.93	0.86-1.00	0.07*
PMI	0.89	0.66-0.97	0.02	0.82	0.68-0.99	0.03*
Male (n = 222)						
Age (per 10-year increase)	1.31	0.89-1.93	0.24			
MELD score	1.03	0.97-1.10	0.33			
Hospitalization status	1.47	0.88-2.46	0.13			
Grade ACLF	1.02	0.64-1.64	0.91			
TPMT/height	0.95	0.88-1.01	0.09	0.95	0.88-1.01	0.09*
PMI	0.83	0.67-1.00	0.08	0.83	0.67-1.00	0.08*
Female (n = 92)						
Age (per 10-year increase)	0.47	0.28-0.83	0.008	0.52	0.29-0.94	0.03
MELD score	0.96	0.89-1.03	0.29			
Hospitalization status	1.64	0.71-3.80	0.25			
Grade ACLF	0.82	0.40-1.70	0.60			
TPMT/height	0.82	0.71-0.95	0.01	0.85	0.73-0.97	0.03*
PMI	0.72	0.61-0.98	0.04	0.88	0.79.-0.99	0.05*

ACLF, acute on chronic liver failure; MELD, model for end-stage liver disease; PMI psoas muscle index; TPMT/height transversal right psoas muscle thickness at the umbilical level/height. Uni and multivariate analysis using the Cox proportional hazards regression models.
*Analyses performed separately to avoid collinearity.

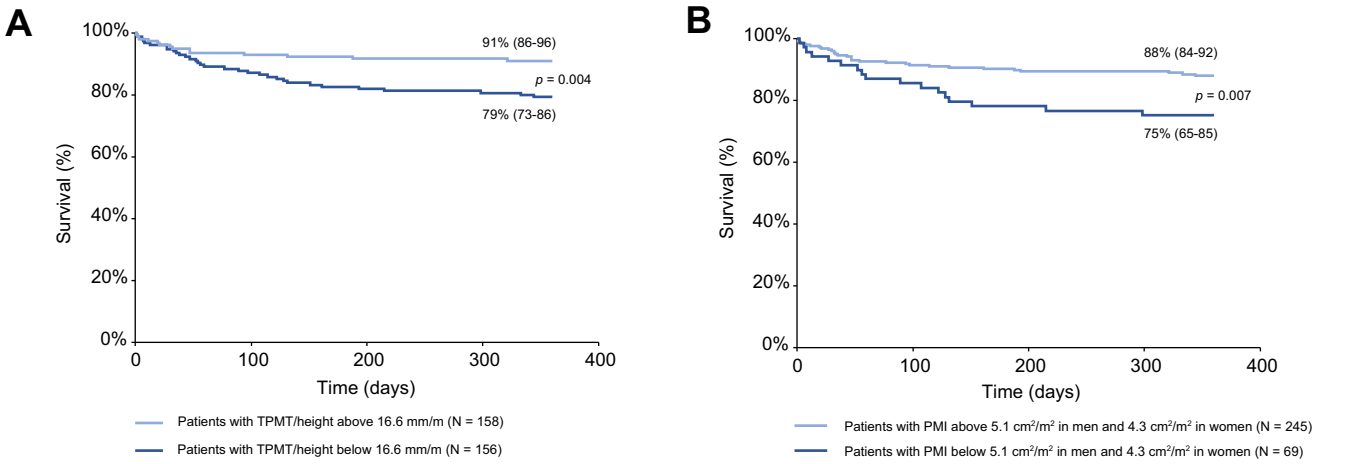

Fig. 1. One-year survival following liver transplantation in patients transplanted with ACLF and an available CT scan performed at LT (±15 days) from our initial cohort (314 patients out of 337 with ACLF).[2] (A) according to the threshold of 16.6 mm/m of TPMT/height[3]; (B) according to the thresholds of 5.1 cm^2/m^2 in men and 4.3 cm^2/m^2 in women of PMI.[4] ACLF, acute-on-chronic liver failure; LT, liver transplantation; TPMT, transversal right psoas muscle thickness at the umbilical level. Survivals were estimated by the Kaplan-Meier method and compared by log-rank test.

umbilicus level, psoas accounting for less than 15% of the total skeletal muscle area *etc*…). It has recently been confirmed that L3-skeletal muscle index (L3SMI) is more strongly correlated with total body protein[5] with less misclassification of mortality risk in patients with cirrhosis.[4] Moreover, patients with higher mortality risk are underestimated using psoas cut-offs. The psoas cut-offs in the present study were mainly used to illustrate the association between TPMT/height and PMI with 1-year mortality.[4] However, even if not ideal, the present study strongly suggests that psoas sarcopenia evaluation is an independent predictor of 1-year mortality in patients with ACLF.

Therefore, we feel that a prospective evaluation of sarcopenia, particularly using L3SMI, should be integrated into the pre-transplant work up of patients with ACLF who are candidates for LT. This would allow us to assess the impact of sarcopenia on outcomes after LT. Finally, sarcopenia parameters could be implemented into a multivariate model to identify patients undergoing potentially inappropriate LT.

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Authors' contributions

Design of the study: FA, CLG, GPG, FS, AL. Acquisition of data: FA, CLG. Statistical analysis: FA, AL. Drafting of the manuscript: FA, CLG, GPG, FS, AL.

Supplementary data

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