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

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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

Figures and tables: 1 and 1

Word count: 1003/800
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 authors must be congratulated for the efforts made in this way. However, the retrospective design of this study and others in the field might bias the analyses, as several variables, considered as important, haven’t been studied yet. Indeed, as highlighted by the authors in the discussion section, the impact of sarcopenia on post-LT outcome wasn’t assessed in this study neither in the available 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 retrospectively assessed on CT-scan 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 cm²/m²) at the L3-L4 level [4]. Age, hospitalization status (home, general ward, intensive care unit), MELD score and grade of ACLF were available for patients at time of LT. We studied the main patient characteristics in ACLF cohort that were associated with one-year survival on univariate and multivariate analysis using the Cox proportional hazards regression models. The overall survival curves at one year were estimated using the Kaplan-Meier method, and were compared using the log-rank test; Statistical testing was done at the two-tailed α level of 0.05. CT-scan allowing 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
TPMT/height was respectively at 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), p<0.0001. PMI was respectively at 6.9 cm²/m² (5.6-8.3) vs. 6.3 cm²/m² (5.1-7.3) vs. 6.1 cm²/m² (5.2-7.4) vs. 5.4 cm²/m² (4.6-6.5), p<0.0001. Uni and multivariate analyses variables associated with 1-year survival in the ACLF cohort are provided in table 1a suggesting 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 cm²/m² in men and 4.3 cm²/m²) in women [4] to identify patients with ACLF with poorer outcome following LT. These thresholds respectively identified two populations with different 1-year survival: 91% (86-96) vs. 79% (73-86), p= 0.004 (Figure 1a) and 88% (84-92) vs. 75% (65-85), p=0.007 (Figure 1b).

In sensitivity analyses according to sex, in cox regression analyses, there was only a trend towards an association of these parameters with 1-year survival in men while the association was independent in women (table 1b and 1c). In the same line, women with low TPMT/height and PMI according to the 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). Men with low PMI had significant lower 1-year survival (76% (63-88) vs. 88% (83-93), p=0.05). Men patients with low TPMT/height experienced 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 as 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 cirrhotic patients in 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 observed acceptable outcome.

Nonetheless, our study has several limitations mainly related to the use of psoas related sarcopenia parameters (variation of umbilicus level, psoas accounting for less than 15% of the total skeletal muscle area etc…). It has been recently confirmed that L3-skeletal muscle index (L3SMI) is more strongly correlated with total body protein [5] with less misclassification of mortality risk in cirrhotic patients [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 to be an independent factor with 1-year mortality in ACLF patients.

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


**Legend to Figure 1:** 1-year survival following liver transplantation in patients transplanted with ACLF and 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 cm²/m² in men and 4.3 cm²/m² in women of PMI [4]
Table 1: Multivariate analysis of factors associated with 1-year mortality in patients with ACLF at time of liver transplantation

<table>
<thead>
<tr>
<th>Covariant</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.11</td>
<td>0.56-1.98</td>
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<tr>
<td>Age (per 10-year increase)</td>
<td>0.92</td>
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<tr>
<td>MELD score</td>
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<tr>
<td>Grade ACLF</td>
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<td>0.64-1.43</td>
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<tr>
<td>TPMT/height</td>
<td>0.92</td>
<td>0.86-0.99</td>
</tr>
<tr>
<td>PMI</td>
<td>0.89</td>
<td>0.66-0.97</td>
</tr>
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</table>

ACLF acute on chronic liver failure; TPMT/height transversal right psoas muscle thickness at the umbilical level/height; PMI psoas muscle index

*analyses performed separately to avoid collinearity.

Table 1b: Multivariate analysis of factors associated with 1-year mortality in patients with ACLF at time of liver transplantation in men (N=222)

<table>
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</thead>
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<td>HR</td>
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<td>Age (per 10-year increase)</td>
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<td>Hospitalization status</td>
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<td>0.88-2.46</td>
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<tr>
<td>Grade ACLF</td>
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<td>0.64-1.64</td>
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<tr>
<td>TPMT/height</td>
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<td>0.88-1.01</td>
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<tr>
<td>PMI</td>
<td>0.83</td>
<td>0.67-1.00</td>
</tr>
</tbody>
</table>

Table 1c: Multivariate analysis of factors associated with 1-year mortality in patients with ACLF at time of liver transplantation in women (N=92)

<table>
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<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (per 10-year increase)</td>
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<td>0.28-0.83</td>
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<tr>
<td>MELD score</td>
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<td>0.89-1.03</td>
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<td>Hospitalization status</td>
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<td>Grade ACLF</td>
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<td>TPMT/height</td>
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<tr>
<td>PMI</td>
<td>0.72</td>
<td>0.61-0.98</td>
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</table>
Figure 1.

a) Patients with TPMT/height above 16.6 mm/m (N=158)
   Patients with TPMT/height below 16.6 mm/m (N=156)

b) Patients with PMI above 5.1 cm²/m² in men and 4.3
   5.1 cm²/m² in women (N=245)
   Patients with with PMI below 5.1 cm²/m² in men
   and 4.3 cm²/m² in women (N=69)

91% (86-96) p=0.004
79% (73-86)

88% (84-92) p=0.007
75% (65-85)