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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.06.006.

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Are liver transplant centres critical for the critically ill patient with cirrhosis?

To the Editor:

We were very interested to read the study by Hernaez, Kramer and colleagues[1] in a recent issue of *Journal of Hepatology*, which examined the prevalence and outcomes of patients with acute-on-chronic liver failure (ACLF) using the US Department of Veterans Affairs database. The authors comprehensively describe the outcomes of 19,082 hospitalised patients with ACLF, compared to 53,234 patients with decompensated cirrhosis without ACLF, over a 10-year period. A key finding was that patients with ACLF admitted to liver transplant centres versus non-transplant centres had 20% and 19% lower odds of dying at 28 days and 90 days, respectively. However, it should be highlighted that firstly, the 28-day odds ratio had a confidence interval that crossed one (odds ratio 0.80, 95% CI 0.61–1.01); and secondly, that there was no difference in the unadjusted 28-day transplant-free mortality between transplant and non-transplant centres when stratifying by presence/absence of ACLF and ACLF grade, as illustrated in Fig. 3 of the manuscript.

We have previously published our experience in Australia and New Zealand, examining the outcomes of 17,044 critically ill cirrhotic patients admitted on a non-elective basis to intensive care units (ICUs) over a 16-year period in comparison to over 775,000 non-cirrhotic patients.[2] Although we were unable to classify patients by the CANONIC or NACSELD definitions of ACLF, we described a robust cohort of cirrhosis patients with SOFA (Sequential Organ Failure Assessment) defined organ failures with an overall transplant-free hospital mortality of 32.4%. We found that for patients with cirrhosis, there was no difference in unadjusted hospital mortality between liver transplant and non-transplant centres (34.2% and 32.1% respectively, $p = 0.06$). Furthermore, transplant centre status did not affect the adjusted annual decline in mortality ($p = 0.27$) or the interaction between the presence of cirrhosis and mortality ($p = 0.06$). We observed that specialist liver transplant ICUs treated patients with higher baseline illness severity scores and liver indices, but this did not affect mortality trends. Until recently, data have been relatively scant regarding liver transplant centre status and its influence on critically ill patients with cirrhosis, however our findings have been consistent with the existing literature.

Therefore, the question of whether liver transplant centre status is important lies within the definitions of ACLF used and the setting of care. As the authors acknowledge, the NACSELD definition of ACLF identifies a more unwell group of patients who would almost invariably need an ICU setting due to the level of organ support required. Using this definition would have excluded more than 4,500 participants in the Hernaez *et al.* study. Alternatively, in the CANONIC definition it could be assumed that many patients with ACLF-1 could be managed on the general ward (*e.g.*, single kidney failure, or liver failure with a creatinine value between 1.5–1.9 mg/dl).

Hence, the authors should clarify whether the NACSELD definition of ACLF or the setting of care (ward *vs.* ICU) alters the mortality benefit offered by liver transplant centres in their dataset. Secondly, clarification is needed regarding which measurable factors the authors believe influenced the mortality benefit in transplant centres in their cohort.

We speculate that some of the mortality benefit seen in the transplant centres may be attributable to more positive attitudes towards ICU admission candidacy and improvements in ward-based management rather than specific ICU management.

We were able to demonstrate the latter in our study but were not in a position to examine factors influencing ICU candidacy, which Hernaez and colleagues may be able to expand upon. Determining the factors and setting by which a mortality benefit was observed may result in better care for patients with ACLF at non-transplant centres and stem the potential tide of ACLF referrals to transplant centres that may flow from the Hernaez *et al.* study.

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

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Reply to: "Prevalence and short-term mortality in a national US cohort with acute-on-chronic liver failure"

Acute-on-chronic liver failure mortality in transplant centers is lower than non-transplant centers

To the Editors:

We appreciate the interest and comments by Dr Majumdar *et al.*[1] In our cohort, the prevalence of acute-on-chronic liver failure (ACLF, based on NASCELD criteria) was 10.3% in transplant centers compared to 9.8% in non-transplant centers. Overall, 28 and 90-day mortality rates were lower in transplant than non-transplant centers (28-day mortality 29.5% *vs.* 33.4%; 90-day mortality 44.3% *vs.* 48.0%, respectively). The adjusted odds ratio of dying from ACLF in transplant centers versus non-transplant centers was 0.79 (95% CI 0.66–0.95) at 28-days and 0.81 (95% CI 0.69–0.96) at 90-days, both estimates adjusted for age, gender, race, etiology, complications of portal hypertension, model for end-stage liver disease-sodium score, triggers of ACLF and facility complexity. Although we did not have unit-specific information, we have ICU complexity built into the facility complexity variable. Our previous report[2] as well as those reported in the current reply to Drs. Majumdar *et al.* show that there was no association between facility complexity and mortality overall; adjusting for facility complexity did not attenuate the effect of transplant centers in our analysis. These data suggest that the observed difference in mortality between patients managed in transplant versus non-transplant centers cannot be fully explained by the ICU complexity and may be related to other unobserved factors, such as early recognition and/or more aggressive management of ACLF in transplant versus non-transplant centers.

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