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Type of organ failure and acute insult have important bearings in outcomes of liver transplantation: A pragmatic discourse

To the Editor:

We read with great interest the study by Thuluvath *et al.* on the role of "Liver transplantation in patients with multiple organ failures: Feasibility and outcomes".[1] In this study they have very nicely demonstrated that prioritizing and expediting liver transplantation in this sickest cohort of cirrhotics is possible and has excellent outcomes in terms of both graft and patient survival at 1 year. This is indeed the need of the hour, and we in principle agree with this approach. However, this issue has been a matter of considerable debate for a substantial period as previous studies have shown dichotomous results.[2–4]

The higher propensity of short-term mortality without transplantation in cirrhotics with multi-organ failures especially with ≥3 organ failures irrespective of the definition used is well established.[5] The rapidly downhill course provides a very small window to transplant, and this study reinforces the fact that the crux lies in the appropriate selection of patients to balance imminent mortality without transplant against peri-transplant complications and overall graft and patient survival after transplantation.[3] However we still have reservations about transplanting patients with multi-organ failures and would like to raise certain pertinent issues concerning the study by Thuluvath *et al.*[1]

Firstly, the authors have pointed out that the type of organ failure had only minimal impact on survival although overall respiratory failure was associated with lower 1-year survival.[1] However, in this study respiratory failure has been defined based on the need for mechanical ventilation and not on respiratory parameters like PaO_2/FiO_2 ratio which are used in the standard definition of respiratory failure. Hence, extrapolating patients who needed mechanical ventilation for non-respiratory causes like grade III and IV hepatic encephalopathy may undermine the effect of pure respiratory failure and its association with 1-year mortality. A previous study by Levasque *et al.* showed that patients with acute-on-chronic liver failure (ACLF) grade 3 had a higher post-transplant mortality (56.7%) than patients with lower grades of ACLF, with more than two-thirds of the patients in that mortality group having a respiratory failure using the standard respiratory failure definitions.[4]

Secondly, the authors have not stratified the patients according to the etiology of acute insult leading to worsening of primary disease and multi-organ failures, which can have an impact on the overall survival.[6] We believe that patients with ACLF behave differently with respect to their natural history depending upon the primary disease as well as the acute insult, for example, alcoholic cirrhosis with alcoholic hepatitis, given time may spontaneously resolve with abstinence and other supportive care while others may not. Furthermore, it would be of interest to know whether the population of cirrhotics with "multiple organ failure" can be considered equivalent to "acute or chronic liver failure" which may provide greater homogeneity in listing patients with ACLF for transplantation. It would be immensely beneficial to the readers if insight into such a sub-group analysis can be done, although we understand the constraints of the authors on account of the database centered retrospective analysis.

We would also be interested in the management of these patients during the interim period of the "window to transplant" in such a large cohort of patients, since sepsis remains a major deterrent to transplant and improvement of organ failures with treatment may improve the overall post-transplant survival, as reported in a recent study by Huebener *et al.*[7]

While this extensive analysis by Thuluvath *et al.*[1] is a source of great optimism in the otherwise gloomy domain of cirrhosis with multi-organ failures, a further stratification with regards to the grey zones mentioned shall add to the robustness of the study.

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Conflict of interest

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Authors' contributions

AR: writing; ST: critical revision.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.09.010.

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Reply to: "Type of organ failure and acute insult have important bearings in outcomes of liver transplantation: A pragmatic discourse"

To the Editor:

We appreciate the comments from Drs. Roy and Taneja regarding our recent publication and thank them for pointing out some of the weaknesses of our study.[1]

One of their criticisms was that our definition of respiratory failure was different from the EASL-CLIF consortium definition, and this is true. We defined respiratory failure as 'the need for mechanical ventilation,' which is similar to that used by the North American Consortium for Study of End-stage Liver Disease (NACSELD).[2] The EASL-CLIF consortium, on the other hand, defined respiratory failure as PaO_2/FiO_2 of ≤200 or SpO_2/FiO_2 of ≤214 or the need for mechanical ventilation.[3] Most patients who meet the criteria for the acute respiratory distress syndrome definition of PaO_2/FiO_2 of ≤200 or SpO_2/FiO_2 of ≤214 would require mechanical ventilation. In our study, it is plausible that a few patients with stage 3–4 hepatic encephalopathy were ventilated for airway protection. Unfortunately, the UNOS database did not provide the reasons for mechanical ventilation, which we highlighted in our discussion. However, 100% of patients who had respiratory failure in our study also had circulatory failure suggesting that these patients were indeed very unstable. It is true that those with respiratory failure had lower 1-year survival (79% *vs.* 81–87% for other organ failures), but 48.7% with respiratory failure had 5–6 organ failures. Nonetheless, we agree with Drs. Roy and Taneja that those with acute-on-chronic liver failure (ACLF) and respiratory failure have lower survival compared to those with other organ failures and it was an independent predictor of post-liver transplant survival as demonstrated in our multivariate analysis (hazard ratio 1.67; 95% CI 1.08–2.77; $p = 0.02$).

Another criticism was that we did not have information on the precipitating causes of liver decompensation. One of the weaknesses of studies using large administrative datasets is the lack of granularity with important variables such as the precipitating causes of ACLF in our study. Although it has been shown that those with infection as a precipitating cause have lower survival without liver transplantation compared to those with other precipitating causes,[4] it is equally true that in the presence of 3 or more organ failures, the survival differences are likely to be minimal irrespective of the precipitating cause. In our study, of the 3,556 patients with 3 or more organ failures, only 8% were alive at 30-days without liver transplantation; in the presence of 4 organ failures (n = 932), only 6% were alive and with 5–6 organ failures (n = 677), only 2% remained alive without liver transplantation. The short median time to death (median 10 days, 95% CI 4–18) or liver transplantation (median 5 days, 95% CI 3–11) after listing in those with 3 or more organ failures further corroborates that the prognosis of these patients is dismal without liver transplantation. It is therefore unlikely that we could prove that precipitating cause may have a major impact on post-liver transplant survival in those with 3 or more organ failures. It would require a substantially larger prospective study.

The third criticism was that patients in our study with multiple organ failures could not be equated with those with ACLF and we had admitted that in our manuscript. In our study, 2,515 patients had 3 or more organ failures at the time of listing, but 3,556 had 3 or more organ failures at transplantation indicating that many of these patients behaved like those with ACLF. Only prospective studies could clearly establish the role of liver transplantation in ACLF, and it is especially true for those with sepsis as the precipitating cause. We hope that there will be further studies to examine these aspects and thank Drs. Roy and Taneja for their comments. Future studies should also examine the costs and post-liver transplant quality of life of patients who were transplanted with multiple organ failures.

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Authors' contributions

Paul Thuluvath, Avesh Thuluvath, Steven Hanish and Yulia Savva contributed to the response.