[6] Kumar D, Vadiraja PK, Nayak B, Thakur B, Das P, Datta Gupta S, et al. Acute on chronic liver failure because of acute hepatic insults: etiologies, course, extrahepatic organ failure and predictors of mortality. J Gastroenterol Hepatol 2016;31:856–864.
[7] Huebener P, Sterneck MR, Bangert K, Drolz A, Lohse AW, Kluge S, et al. Stabilisation of acute-on-chronic liver failure patients before liver transplantation predicts post-transplant survival. Aliment Pharmacol Ther 2018;47:1502–1510.

Akash Roy
Sunil Taneja*
Department of Hepatology, Postgraduate Institute of Medical Education & Research, Chandigarh, India
*Corresponding author. Address: Department of Hepatology, PGIMER, Chandigarh, India;
Tel.: +91 9592160444; Fax: +91 1722756344.
E-mail address: drsuniltaneja@hotmail.com

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.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interests

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

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

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

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.013.

References

[1] Thuluvath PJ, Thuluvath AJ, Hanish S, Savva Y. Liver transplantation in patients with multiple organ failures: feasibility and outcomes. J Hepatol 2018;69:1047–1056.

[2] Bajaj JS, O'Leary JG, Reddy KR, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology 2014;60:250–256.

[3] Hernaez R, Sola E, Moreau R, Gines P. Acute-on-chronic liver failure: an update. Gut 2017;66:541–553.

[4] O'Leary JG, Reddy KR, Garcia-Tsao G, et al. NACSELD Acute-on-Chronic Liver Failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology 2018, Jan 8 [Epub ahead of print].

Paul J. Thuluvath[1,3,*]
Avesh J. Thuluvath[2]
Steve Hanish[3]
Yulia Savva[1]

[1]*Institute of Digestive Health & Liver Diseases, Mercy Medical Center, Baltimore, MD, United States*
[2]*Johns Hopkins University School of Medicine, Baltimore, MD, United States*
[3]*University of Maryland School of Medicine, Baltimore, United States*
*Corresponding author. Address: Institute of Digestive Health & Liver Diseases, Mercy Medical Center, Baltimore, MD 21202, United States.
E-mail address: thuluvath@gmail.com

Only in the darkness can you see the stars: Severe alcoholic hepatitis and higher grades of acute-on-chronic liver failure

To the Editor:

We read with interest the recently published study by Sersté *et al.* in the *Journal*, as well as the subsequent correspondences by Forrest *et al.* and the original authors.[1,2] Both the study and subsequent correspondences agreed on to 2 important aspects in severe alcoholic hepatitis (SAH) related acute-on-chronic liver failure (ACLF): i) the benefits of corticosteroids (CS) for SAH in patients with ACLF grades 2 and 3 and ii) the dire need for new clinical trials in this difficult to treat group of patients. With this in mind, we would like to briefly discuss salient aspects in literature with regards to key studies in ACLF and provide novel insights into future prospects based on our experience with faecal microbiota transplantation (FMT) in this group of patients. Gustot *et al.* demonstrated that ACLF grade 2 and 3 patients (any cause) had a 180-day mortality approaching 79% and 96% in which, early 28-day liver transplantation (LT) improved survival in 80% at 180 days and 75% at 1 year.[3] In those without LT and <4 organ failures (OFs) and Chronic Liver Failure Consortium (CLIF-C) ACLF score <64, continuation of standard care resulted in survival in only 39% with 100% mortality in those with >4 OFs or CLIF-C ACLF score >64. Similarly, Sersté *et al.* show that ACLF in SAH is associated with a poor outcome and that the Lille response to corticosteroids was reduced in those with prevalent ACLF.[1] Forrest *et al.* reveal that for Lille-non-responders with ACLF grades 0, 1 and (2+3) the 90-day survival rates were 68.1%, 45.8% and 36.7%.[2] Corticosteroid use may also promote infections in ACLF leading to Lille non-response and worse outcomes.[4] Considering this 'catch-22' situation, we retrospectively looked at 1.5-year outcomes in patients with SAH-ACLF and infections not eligible for CS and not undergoing LT who were on salvage FMT. Written informed consent was obtained from each patient included in the study and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee. From August 2016 to September 2018, 88 patients with SAH-ACLF underwent FMT as per previously described and published protocol of which 72 patients completed treatment.[5,6] The complete patient enrolment into the study along with exclusion details is shown (Fig. S1). Thirty-eight patients completed 1.5-year (548 day) follow-up, of whom 15 were excluded in view of alcohol relapse (n = 9), use of complementary and alternative medication (n = 4) and LT (n = 2). Finally, 23 patients were included in the analysis. For ease in analysis, patients with ACLF were grouped into lower (0+1) and higher (2+3) grades. All were males with mean age 46.5 ± 9.2 years; ACLF grade 0 (n = 2, 8.7%), grade 1 (9, 39%), grade 2 (9, 39%), grade 3 (3, 13%); mean CLIF-C ACLF score 93.6 ± 9.2; CLIF-C Score 11.7 ± 1.7; Child Pugh score 12.4 ± 1.2; discriminant function 78 ± 17.2 (range 53.4 to 119.4) and model for end-stage liver disease-sodium (MELD-Na) 29.5 ± 3.7. At the end of 548 days follow-up, 8 patients (overall survival rate 66%) died with overall mean survival 389.3 (95% CI 295.4 to 483.1) days. The commonest cause of death on follow-up was sepsis (n = 5/8, 62.5%). Two patients developed culture negative neutrocytic bacterascites controlled with a short course of intravenous antibiotics while another developed uncontrolled acute variceal bleeding after completion of FMT. In the lower (ACLF 0+1, n = 11) and higher grades (ACLF 2+3, n = 12), the proportion of patients surviving (Fig. 1) at the end of 548 days follow-up was 72.7% and 58.3%, respectively (χ^2 0.2761, $p = 0.59$). Hughes *et al.* demonstrated that there has been no improvement in mortality from AH because of the lack of effective treatments in this patient group.[7] We believe that healthy donor FMT may be a potential treatment option that requires further prospective high-quality studies for SAH and higher grades of ACLF. The results of ongoing randomized trial comparing CS to FMT in SAH-ACLF are highly anticipated (NCT03091010). Even though a small retrospective observation with confounding factors, following a crude protocol that requires refinement, we modestly ponder the hopeful aspect of this intervention. Many patients were excluded in

Keywords: FMT; Dysbiosis; Stool transplant; ACLF; Portal hypertension; Alcohol; Cirrhosis; Gut microbiome; Microbiota.