

Waiting list priority for patients with acute-on-chronic liver failure: Not just horseplay

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List of Abbreviations:

Acute on chronic liver failure (ACLF)
Liver transplantation (LT)
United Network for Organ Sharing (UNOS)

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Acute on chronic liver failure (ACLF) is a syndrome of systemic inflammation and multiple organ system failures that is associated with a significantly high 28-day mortality ranging from 15-89%,(1) and which is increasing in prevalence in the United States and globally.(2) Although several definitions for ACLF exist, it is generally agreed upon that this condition yields greater non-transplant mortality than mere decompensated cirrhosis. The EASL-CLIF definition of ACLF categorizes patients according to the number of organ failures present, specifically as 1 organ failure (ACLF-1), 2 organ failures (ACLF-2) and 3 or more organ failures (ACLF-3).(1) Liver transplantation (LT) remains the only life-saving intervention in this population, especially among those with ACLF-3.

Previously, studies exploring the role of LT in the setting of ACLF were limited to a small sample size, even if performed at the multi-center level. Since 2018, however, several papers have been published utilizing the United Network for Organ Sharing (UNOS) database, allowing for the study of thousands of patients listed or transplanted with ACLF, including ACLF-3. The editorial by Goldberg and Bajaj in this issue of Liver Transplantation provide only one perspective about what has been learned from UNOS database in relation to the role of liver transplantation in ACLF patients. In this editorial, we discuss the important observations that were made from the studies analyzing the UNOS database, subsequent validation of these findings, limitations of the information provided by these investigations, and how the preliminary data generated by analysis of the UNOS database has contributed to the design of the prospective CHANCE study, that aims to address unanswered questions in the field of transplantation for ACLF.

Important observations from the UNOS database and subsequent corroboration

Current organ allocation policy in the United States and Europe is based on the Model for End-Stage Liver Disease (MELD) score and Model for End-Stage Liver

Disease-Sodium (MELD-Na) score, which prioritizes patients with decompensated cirrhosis according to expected 90-day mortality. There are no specific exception points for ACLF patients, partially due to the lack of consensus regarding how to define it. Subsequently, patients with ACLF are ranked on the waiting list based on their MELD or MELD-sodium score, regardless of the number of organ failures which have developed.

In the seminal study from the UNOS database addressing the role of LT in patients with ACLF, mortality on the waiting list was assessed in approximately 79,000 patients, including more than 5,000 patients with ACLF-3. Two important findings were demonstrated from this investigation.(3) First, using competing risks regression analysis, with LT as the competing event, the 1-year cumulative incidence of death or waitlist removal due to being too sick for LT increased with worsening grade of ACLF, with a significant rise in mortality among candidates listed with ACLF-3, approaching 20% at 6 months and 30% at 1 year.(3) (figure 1a) This finding has been subsequently validated in a retrospective, multi-center European study of over 300 patients who developed ACLF either at listing or afterwards,(4) with a total of 131 patients studied with ACLF-3 prior to LT. The cumulative incidence function, as based on competing risks regression, similarly revealed greater probability of death on the waiting list with worsening grade of ACLF. Patients with ACLF-3 also had a more than 30% likelihood of waitlist mortality within 6 months of listing.(4) (Figure 1b)

Another substantial observation from this study was that the MELD and MELD-Na scores underestimated waitlist mortality with increasing grades of ACLF. Figure 2a displays 90-day mortality from listing as obtained from the UNOS database, categorized by different grades of ACLF and subcategorized according to MELD-Na category at waitlist registration. The analysis of waiting list mortality according to ACLF grade at listing indicated that highest risk of death or removal from the waiting list belonged to

patients with ACLF-3 and MELD-Na scores <25, followed by candidates with ACLF-2 and MELD-Na scores <25 at listing.(3) (Figure 1c) These findings not only suggest that the MELD-Na score underestimates mortality among patients with ACLF-2 or ACLF-3, but also implies that the presence of organ failures not captured by the MELD-Na score contributes significantly to death on the waiting list. A separate study to validate these results was performed by Hernaez et al through analysis of over 70,000 patients from 127 Veterans Administration hospitals.(5) Findings from this study similarly demonstrated the underestimation of patient mortality by the MELD-Na score in the setting of ACLF. (Figure 1d) Furthermore, the discrepancy between expected mortality according to the MELD-Na score and actual mortality widens with increasing grade of ACLF, thereby providing convergent validity to those of the UNOS database study. The relevant observations from additional studies regarding LT for patients with ACLF, along with corroborating data, are displayed in Table 1.

Limitations of the UNOS database

Though several conclusions based on investigation of the UNOS database have been subsequently verified, there are important limitations which should be discussed. The initial purpose of the UNOS registry studies was to generate hypotheses based on longitudinal observations of a large patient sample, which require subsequent testing. The primary limitation, though, is due to the potential for misclassification of ACLF grade. The registry contains information to identify liver, coagulation and renal failure based on laboratory parameters. In addition, data are available regarding the presence grade 3-4 hepatic encephalopathy at listing and transplantation, which allows the identification of brain failure per the EASL-CLIF criteria. Circulatory and respiratory failure, though, are identified based on surrogates of vasopressor support and mechanical ventilation, and the indication for these interventions is not definitive. It is

therefore possible that certain patients who do not have circulatory or respiratory failure are incorrectly classified as having them, such as those who are intubated for airway protection. However, it is of paramount importance to discuss whether these limitations affect the conclusions of the studies. For the purpose of studying waitlist mortality, we believe that although misclassification is feasible, it would actually lead to underestimation of the probability of death on the waiting list, as determined by UNOS analyses. Specifically, the conclusions of the studies regarding waitlist mortality were centered around patients with ACLF-3, a group which has consistently been demonstrated to have the highest mortality risk in multiple prospective trials. Incorrectly categorizing certain patients as having ACLF-3, therefore, may lead to inclusion of patients with lower ACLF grades into the analysis and subsequently reducing the estimated mortality. We believe it is unlikely that misclassification would overestimate the observed mortality from the UNOS database, as the phenotype of a “high-mortality non-ACLF” patient does not exist.(6)

The global CHANCE study to address the unanswered questions

Although the studies from the UNOS database have revealed important observations in relation to transplantation for ACLF, prospective validation of these findings is necessary to advance the field. In this context, the EASL-CLIF Consortium in collaboration with the International Liver Transplantation Society (ILTS) and the European Liver and Intestine Transplant Association (ELITA) have designed prospective non-interventional observational global study (CHANCE, liver transplantation in patients with Cirrhosis and severe ACLF: iNdications and outcome, ClinicalTrials.gov: NCT04613921). The international nature of the CHANCE study will allow assessments of the different regional/national allocation systems on waitlist mortality and post-transplant outcomes.

Conclusion

In conclusion, transplantation for patients with ACLF, and particularly ACLF-3, is highly complicated, and relevant questions surrounding waiting list mortality are only beginning to be addressed. Investigation of the UNOS database has yielded important information that has been corroborated in subsequent studies and has provided the basis for changes in organ allocation policy in countries such as the UK and Spain, which have already made recommendations to allow prioritization of organ to transplantation patients with severe ACLF. Importantly, the UNOS database has provided has provided the foundation upon which future research, such as the CHANCE study, is being built.

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Figure Legends

Figure 1a. Cumulative incidence of waitlist mortality according to ACLF grade, per the UNOS database

Figure 1b. Cumulative incidence of waitlist mortality according to ACLF grader, per the ELITA study

Figure 1c. 90-day mortality or removal from the waiting list according to ACLF grade and MELD-Na score (UNOS database)

Figure 1d. 90-day mortality according to ACLF grade and MELD-Na score (Veterans Administration database)

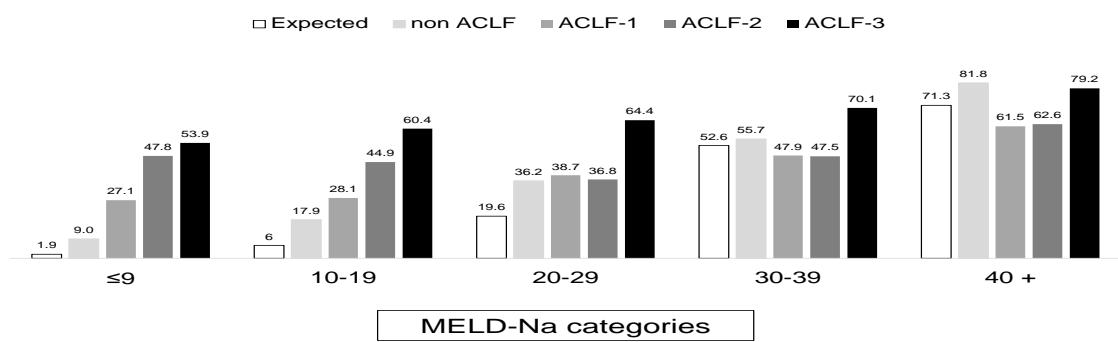
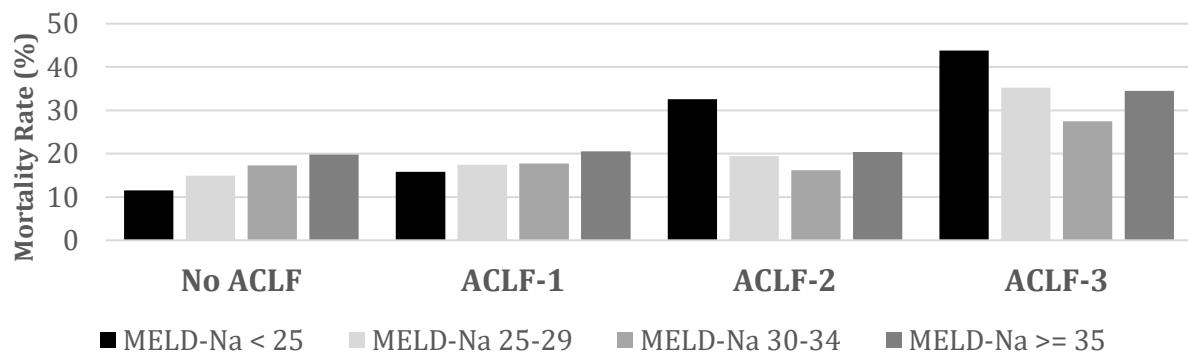
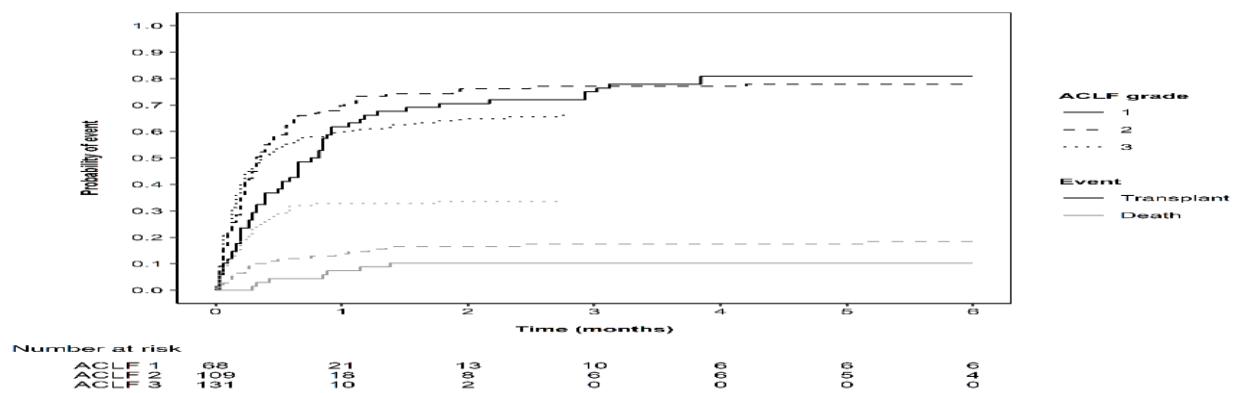
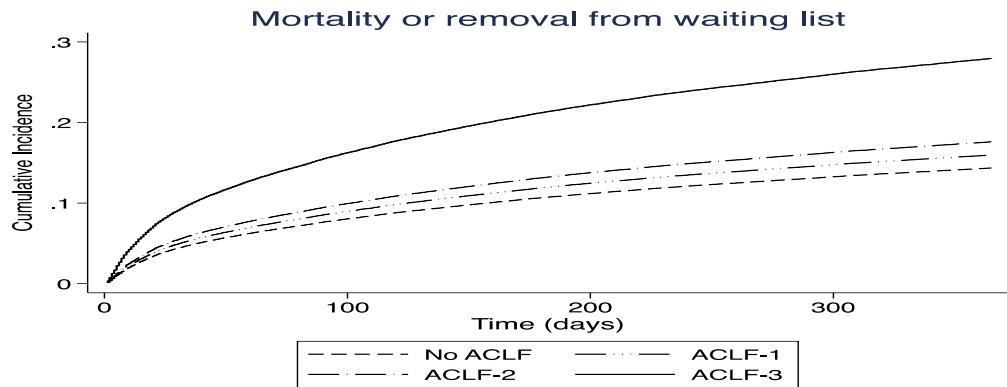


Table 1. Summary of studies from the UNOS database regarding waitlist and post-transplant outcomes in patients with severe ACLF

Study (Year)	Type of Study	Total Patients with ACLF-3	Significance	Corroborating Studies
Sundaram (2019) (3)	UNOS database years, 2005 to 2016	,355 at listing 6,381 transplanted	Identified > 80% 1-year survival after, including among patients with ACLF-3	Belli et al (4)
Sundaram (2019) (3)	UNOS database years, 2005 to 2016	5,355 at listing 6,381 transplanted	Demonstrated waitlist mortality is highest among ACLF-3 patients regardless of MELD-Na Identified presence of mechanical ventilation as strongest predictor of post-LT mortality	Belli et al (4) Hernaez et al (5) Artzner et al (7)
Sundaram (2019) (8)	UNOS database, years 2004-2017	3,636 patients listed with ACLF-3	Improvement in ACLF grade increases survival after liver transplantation	Heubener et al (9)