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Factors Associated with Survival of Patients With Severe Acute on Chronic Liver Failure Before and After Liver Transplantation

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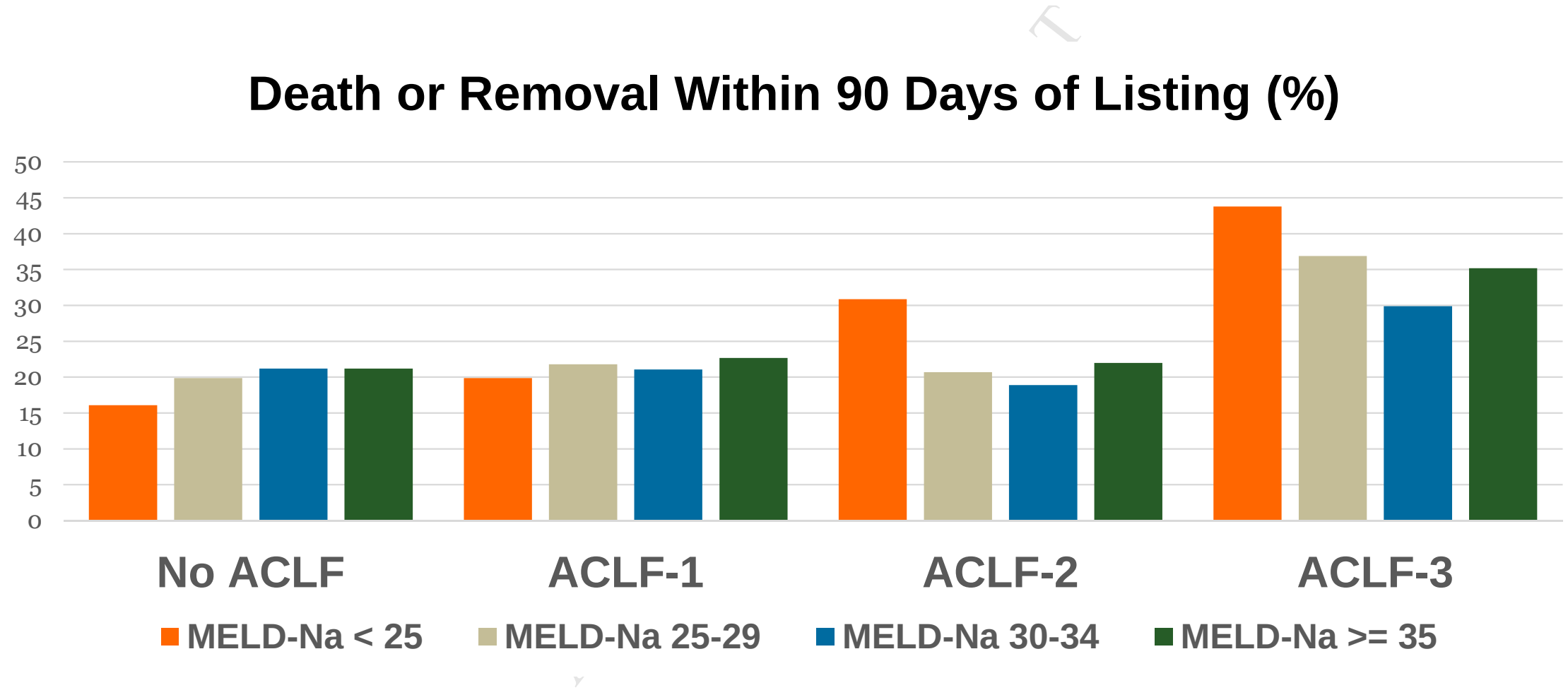

Title: Factors Associated with Survival of Patients With Severe Acute on Chronic Liver Failure Before and After Liver Transplantation

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List of Abbreviations:

Acute on chronic liver failure (ACLF)

Alcoholic liver disease (ALD)

Donor risk index (DRI)

Hepatitis C virus (HCV)

Karnofsky Performance Status (KPS)

Model for end-stage liver disease (MELD)

Model for end-stage liver disease-sodium (MELD-Na)

United Network for Organ Sharing (UNOS)

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Abstract

Background & Aims: Liver transplantation for patients with acute on chronic liver failure with 3 or more failing organs (ACLF-3) is controversial. We compared liver waitlist mortality or removal according to model for end-stage liver disease (MELD) score vs ACLF category. We also studied factors associated with reduced odds of survival for 1 year after liver transplantation in patients with ACLF-3.

Methods: We analyzed data from the United Network for Organ Sharing from 2005 through 2016. We identified patients who were on the waitlist (100,594) and those who received liver transplants (50,552). Patients with ACLF were identified based on the EASL-CLIF criteria. Outcomes were evaluated with competing risks regression, Kaplan-Meier analysis, and Cox proportional hazards regression.

Results: Patients with ACLF-3 were more likely to die or be removed from the waitlist, regardless of MELD-Na score, compared to the other ACLF groups; the proportion was greatest for patients with an ACLF-3 score and MELD-Na score below 25 (43.8% at 28 days). Mechanical ventilation at liver transplantation (hazard ratio [HR], 1.49; 95% CI, 1.22–1.84), donor risk index above 1.7 (HR, 1.22; 95% CI, 1.09–1.35), and liver transplantation within 30 days of listing (HR, 0.89; 95% CI, 0.81–0.98) were independently associated with survival for 1 year after liver transplantation

Conclusions: In an analysis of data from the United Network for Organ Sharing registry, we found high mortality among patients with ACLF-3 on the liver transplant waitlist—even among those with lower MELD-Na scores. So, certain patients with ACLF-3 have poor outcomes regardless of MELD-Na score. Liver transplantation increases odds of survival for these patients, particularly if performed within 30 days of placement on the waitlist. Mechanical

ventilation at liver transplantation and use of marginal organs were associated with increased risk of death.

KEY WORDS: UNOS database; DRI renal failure; MELD score

Introduction

Acute on chronic liver failure (ACLF) is a syndrome characterized by acute hepatic decompensation, organ system failures, and 28-day mortality of greater than 15%.[1] ACLF grade 3 (ACLF-3), defined as the development of three or more organ failures,[2] has an associated mortality without liver transplantation approaching 80% at 28-days and greater than 90% at one year, indicating a very poor prognosis.[1–4]

Considering the high mortality associated with ACLF-3, liver transplantation represents a potentially important intervention for these patients. Nonetheless, additional information is needed regarding transplantation for this population, in terms of priority on the waitlist and post-transplant survival. For instance, it has been suggested that the development of extra-hepatic ACLF, consisting of circulatory, renal, neurologic or respiratory failure, is physiologically distinct from and yields a higher mortality then hepatic ACLF, due to liver or coagulation failure.[5] As the model for end-stage liver disease (MELD) score or its extension MELD-Sodium (MELD-Na) does not capture several of these extra-hepatic organ failures, it is feasible that certain patients with ACLF-3 may have a high short-term mortality regardless of their MELD or MELD-Na score. Such patients may have a survival benefit by receiving greater priority on the waiting list.

Additionally, studies regarding liver transplantation in patients with ACLF-3, have demonstrated a 1-year post transplant survival greater than 80%, though several of these have been retrospective analyses of small numbers of patients with ACLF-3.[3,4] A recent registry analysis revealed a one-year post-transplant survival of greater than 80% for patients with ACLF-3, though this analysis was restricted to those transplanted within 30 days from waitlist registration.[6] Despite the limitations, these findings suggest transplantation for ACLF-3 may not be an "exercise in futility." However, given the limited availability of donor organs, the benefit of transplantation in ACLF-3 must also be balanced against the risk of poor post-transplant outcomes. Further research is therefore warranted regarding which recipient and donor factors affect post-transplant survival among patients with ACLF-3, to aid the clinician in determining

who may and may not benefit from organ transplantation.

To address these issues, we performed an analysis of the United Network for Organ Sharing (UNOS) database. Our first aim was to determine waitlist mortality for different grades of ACLF and compare this to mortality associated with increasing MELD-Na scores. We hypothesized that the waitlist mortality associated with ACLF-3 would be greater than among those without ACLF-3, regardless of MELD-Na score category. Secondly, we sought to define which characteristics of transplanted patients with ACLF-3 were associated with greater post-transplant survival including the presence/absence of specific organ failures, transplantation within 30 days of listing,[4,6] frailty as measured by Karnofsky Performance Status (KPS) at transplantation,[7] donor risk index (DRI),[8] and futility risk score.[9]

Patients and Methods

The study protocol was approved as exempt from review by the institutional review board at Cedars-Sinai Medical Center. The study and analysis of this study was performed consistent with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

United Network for Organ Sharing (UNOS) database analysis

From the UNOS registry, we evaluated patients age 18 or older listed for liver transplantation from 2005 to 2016. Patients with acute or fulminant liver failure or who had hepatocellular carcinoma at the time of waitlist registration were excluded. We collected data regarding patient characteristics at the time of waitlist registration and both patient and donor organ characteristics at transplantation.

Identification of ACLF

The study population was categorized as having ACLF at the time of waitlist registration or liver transplantation based on the EASL-CLIF criteria of having a single hepatic decompensation such as ascites, hepatic encephalopathy, variceal bleed, or bacterial infection and one of the following organ failures: single renal failure, single non-renal organ failure with renal dysfunction or hepatic encephalopathy, or two non-renal organ failures.[10] (Table S1) Given the lack of necessary data to assess for organ failure at time of waitlist removal or death, we were unable to evaluate for presence of ACLF at these time points. Regarding decompensating events, we assessed for the presence of ascites or hepatic encephalopathy, as information regarding variceal hemorrhage and bacterial infection were unavailable. Specific organ failures were determined according to the chronic liver failure (CLIF) consortium organ failures score for coagulopathy, liver failure, renal dysfunction and renal failure, neurologic failure, and circulatory failure.[10] We used mechanical ventilation as a surrogate marker for respiratory failure.

Karnofsky Performance Status

In order to assess whether frailty is associated with post-transplant outcomes for patients with ACLF-3, we determined KPS scores at the time of liver transplantation. The KPS is an assessment of a patient's functional status, scored from 0-100%, where 100% is normal activity and 0% indicates death,[11] which predicts mortality after liver transplantation. Patients were categorized into either low-intermediate performance status (0-70%) or high performance status (80-100%), based on prior data demonstrating the association between KPS scores less than 80% and post-transplant mortality.[7]

Futility Risk Score

A study by Asrani et al. evaluated recipient variables associated with patient death and graft failure after liver transplantation, among non-hepatitis C infected patients.[9] Their scoring system, named the futility risk score, utilizes recipient factors including need for ventilator support, age > 60 years, hemodialysis, diabetes, or serum creatinine >= 1.5 mg/dl. A score > 8 points indicates a less than 50% likelihood of long-term graft survival. We sought to determine whether this risk score could be applied to risk stratifying patients with ACLF-3 needing liver transplantation. Patients were categorized as low (<= 8 points) or high (> 8 points) futility risk score.

Outcomes

In our evaluation of patients listed for liver transplantation, we compared one-year waitlist mortality among the different grades of ACLF. *We combined death and waitlist removal from being too sick into a single outcome* to reduce the bias in the estimates of waitlist mortality, since the primary reason patients are removed from the list is due to clinical deterioration.[12] Additionally, we compared 28-day and 90-day survival among patients with different ACLF

grades at listing, across the following MELD score categories: < 25, 25-29, 30-34, and >= 35. For our assessment of patients post-liver transplantation, the primary outcome was patient survival at one-year, as we believed the greatest impact of ACLF presence on survival will be early after liver transplantation.

Statistical analysis

Comparisons were made utilizing Chi-square testing for categorical variables and analysis of variance or Kruskal-Wallis testing for continuous variables. In the pre-transplant cohort, waitlist mortality or removal among the different ACLF groups were compared using Fine and Gray competing risks regression, with creation of a cumulative incidence function. Differences between cumulative incidence functions were determined using log-rank testing. Comparisons regarding waitlist mortality/removal across ACLF and MELD-Na score categories were evaluated with Chi-square testing.

In the post-transplant cohort, survival probability was evaluated with Kaplan-Meier methods, with differences in survival probabilities assessed by log-rank testing. Predictors of post-transplant mortality were determined with multivariable Cox proportional hazards modeling. Independent variables were selected a priori, based on hypothesized clinical significance. The final multivariable model was determined using manual backwards selection, with p-value <0.10 on univariable analysis considered significant for inclusion. Variables were additionally removed after testing for co-linearity, as determined by a variance inflation factor greater than ten. Risk related to post-transplant mortality was expressed as hazard ratios (HR) with 95% confidence intervals. Goodness of fit was determined using Cox-Snell residuals. All statistical analyses were performed using the Stata statistical package (version 14, Stata Corporations, TX).

Results

Outcomes after waitlist registration

Study population characteristics

Table 1 describes the full study population of patients at waitlist registration, stratified by ACLF category. A total of 100,594 patients were identified, of which 79,520 (79.1%) did not have ACLF, 9,640 (9.6%) patients had ACLF-1, 6,079 (6.0%) had ACLF-2, and 5,355 (5.3%) had ACLF-3. Patients with ACLF-1 were the oldest and had the greatest proportion of males, while those without ACLF had the highest proportion of Caucasians. Body mass index (BMI) was similar among all patient categories. Regarding etiology of liver disease, patients with ACLF-2 had the greatest percentage of alcoholic liver disease (ALD), whereas those without ACLF had a larger proportion of hepatitis C virus (HCV). As expected mean MELD and MELD-Na score was higher with increasing grade of ACLF. Interestingly, albumin level was highest in ACLF-3, though this may reflect administration of intravenous albumin to those patients.

Waitlist survival among ACLF groups

Figure 1 depicts the cumulative incidence of one-year mortality after waitlist registration among the study cohort. Probability of mortality within one year after listing was significantly greater for patients with ACLF-3 than the other groups ($p<0.001$). In Figures 2a and 2b, we subsequently display the proportion of patients who died or were removed within 28 and 90 days of listing, according to ACLF grade and MELD score category. Patients with ACLF-3 were most likely to die or be removed across all MELD categories, though the proportion was greatest among those with ACLF-3 and MELD score less than 25 (43.8% at 28 and 90 days). Patients without ACLF but MELD score >= 35 had a significantly lower percentage of patients who died or were removed from the waitlist, as compared to ACLF-2 and patients with ACLF-3, with MELD scores < 25 ($p<0.001$). Table S2 provides further details regarding waitlist mortality among the different ACLF categories according to both MELD and MELD-Na score.

Outcomes after transplantation

Recipient and donor characteristics at transplantation

We identified a total of 50,552 patients who met our inclusion criteria at the time of transplantation, of which 29,283 (57.9%) had no ACLF, 7,375 (14.6%) patients had ACLF-1, 7,513 (14.9%) patients had ACLF-2, and 6,381 (12.6%) patients had ACLF-3. Regarding demographic data, patients with ACLF-3 had the smallest proportion of males (62.8%), the fewest percentage of Caucasians (65.9%), and greatest proportion of Hispanics (19.1%). The percentage of patients with ALD was highest among ACLF-2 (35.1%) and patients with ACLF-3 (34.9%), while the prevalence of HCV-induced cirrhosis was lowest in these patient groups. Mean MELD-Na score at transplantation was significantly greater among patients with ACLF-3 (37.4). Among the patients with ACLF-3, 3,583 (56.2%) had three-organ failure alone, whereas 1,646 patients (25.9%) had four-organ failure, 866 patients (13.6%) had five-organ failure, and 286 patients (4.5%) had six-organ failure. (Table 2)

Data were also compared regarding donor characteristics of the transplanted patients. (Table 2) patients with ACLF-3 received younger donor organs (mean age 38.7 years), fewer organs from diabetic donors (8.8%), greater percentage of organs from donors dying of head trauma (38.0%), and the smallest percentage of organs from high risk donors with DRI >= 1.7 (22.9%).

One-year post-transplant survival for ACLF-3

After transplantation, one-year survival was lowest among patients with ACLF-3 (81.8%) compared to the other patient groups (88.1-91.9%, $p<0.001$). (Figure S1, Table S3). In table 3, we compare the recipient and donor characteristics of the 5,224 patients with ACLF-3 who survived and the 1,157 patients who died at one year post-liver transplantation. Among the population of patients with ACLF-3, those who survived were younger (51.7 vs 52.9 years) than those who died, but were otherwise similar regarding sex, race/ethnicity, and MELD score.

However, etiology of liver disease was different between the groups, as alcoholic liver disease was more prevalent among those who survived within one year (36.5 vs 27.3%) whereas HCV was more common among those who died (41.8 vs 32.3%). We further compared KPS, futility risk index, DRI, and transplantation within 30 days of listing among those who survived and died at one year after transplantation. Patients who were alive at one year had a greater prevalence of KPS above 80%. The percentage of patients with high liver futility index (score > 8) and high DRI (>= 1.7) was lower among those who survived, while the proportion of patients receiving liver transplantation within 30 days was greater among patients alive at one year after transplant.

Organ failure

Patients who survived for one-year post-liver transplantation had lower prevalence of need for mechanical ventilation (33.1 vs 49.0%, p<0.001) and circulatory failure (49.8 vs 60.6%, p<0.001). However, the prevalence of coagulation failure (65.6 vs 54.5%, p<0.001) was greater among those who survived after liver transplantation. The prevalence of renal failure, liver failure, and neurologic failure were similar between the two patient groups. Expectedly, the prevalence of four or more organ failure was lower among patients who survived (42.3 vs 50.7%, p<0.001). (Table 3)

Post-transplant survival probability

In Supplemental Table 4, we display survival at one year post-liver transplantation survival probabilities, according to patient and donor variables among patients with ACLF-3. The largest difference in survival probability was based on the presence or absence of need for mechanical ventilation (Figure 3a), with 85.4% one-year survival among those not mechanically ventilated at liver transplantation compared to 75.3% with who were mechanically ventilated. The one-year survival of 85.4% numerically approaches that of no ACLF (91.9%), ACLF-1 (89.1%), and ACLF-2 (88.1%) patients receiving liver transplantation. (Figure 3b) Notably, the

presence of respiratory failure appeared to have greater impact on survival than the development of more than three organ failures.

Additionally, the use of a marginal donor organ (DRI >= 1.7) led to reduced one-year survival post-liver transplantation (78.1%), though transplantation with an optimal organ yielded a survival probability of 82.9%. Liver transplantation within 30 days from listing also yielded greater survival (82.5%) as opposed to outside of 30 days (79.4%). (Figures S1-S4) When analyzing outcomes for patients with ACLF-3 with need for mechanical ventilation (Figures 3c and 3d), we demonstrated greater one-year survival with use of a low-risk organ (76.5%) versus sub-optimal organ (71.6%) (p=0.034), along with greater survival when transplanted within (76.5%) or after (73.3%) 30 days from listing (p=0.032).

Cox proportional hazards analysis

Univariable and multivariable Cox proportional hazards regression regarding post-transplant mortality are displayed in Table 4. On univariable analysis, high DRI and futility risk score, transplantation within 30 days from listing, and presence of respiratory failure, circulatory failure, and four or more organ failures were associated with one-year mortality. However, on multivariable analysis, only the need for mechanical ventilation (HR=1.49; 95% CI 1.22-1.84) or a sub-optimal donor organ (HR=1.22; 95% CI 1.09-1.35) predicted increased risk of mortality, whereas transplantation within 30 days from listing was associated with reduced mortality (HR=0.89; 95% CI 0.81-0.98) within one year after transplantation. The mean variance inflation factor for the model was 1.69, indicating no co-linearity.

Sub-group analysis of ACLF-2

Given the greater incidence of mortality or waitlist removal among ACLF-2 patients with lower MELD scores, compared to those without ACLF but higher MELD scores (supplemental table 2), additional analysis was performed among these patients regarding the prevalence of organ failures associated with waitlist and post-transplant mortality. In table S5, we compare the prevalence of organ failures at waitlist registration. Patients who died or were removed within 90

days had a greater prevalence of renal and neurologic failure, whereas those who survived or were transplanted had a higher prevalence of coagulation failure. Both groups had a similar prevalence of liver failure. Additionally, circulatory failure and mechanical ventilation were also similar in prevalence, though there were relatively few patients in either group with these conditions. In our analysis comparing patients with ACLF-2 who died or survived at one year after liver transplantation (table S6), there was greater prevalence of renal failure, circulatory failure, and mechanical ventilation at liver transplantation among patients with one-year post-transplant mortality, whereas liver failure and coagulation failure were more prevalent among those who survived beyond one year. Multivariable analysis revealed that organ failures with significant association with mortality within one year after liver transplantation included renal failure, circulatory failure, and mechanical ventilation at the time of transplantation (table S7).

Discussion

In this study of transplantation for ACLF patients, we report several important findings regarding pre- and post-transplant outcomes. In the analysis of waitlist outcomes, we determine that even at a MELD score < 25, the short-term mortality among certain patients with ACLF-3 approached 44%; this was significantly greater than that seen among patients with a MELD score >= 35 but without ACLF. This indicates that ACLF classification may help identifying patients who are at risk of high short-term mortality. We believe there are two reasons for this. First, as would be expected, patients in this subgroup would receive fewer organ offers as they have lower priority on the waiting list. Additionally, the MELD score, though very well-validated to identify patients at risk of death from end-stage liver disease and guide organ allocation policy,[13] is designed to evaluate organ failure from hepatic and renal dysfunction; as such patients with ACLF-3 with a low MELD score would by necessity have some combination of respiratory, neurologic, or circulatory failure. As demonstrated by Shi and colleagues, ACLF due to extra-hepatic organ failures is a physiologically distinct entity from ACLF secondary to hepatic failure, leading to a lower 90-day and one-year non-transplant survival in the former. Such patients may therefore be "sicker than their MELD score." Although the reason is not fully elucidated, studies have shown a greater incidence of bacterial infection as the primary insult in extra-hepatic ACLF,[5] and that ACLF occurring in patients with prior hepatic decompensation tended to be less severe.[10] Nonetheless, we believe our study results suggest that patients with ACLF-3 with organ failures not reflected by the MELD score may benefit from additional priority on the waiting list, to facilitate earlier transplantation. These findings regarding the value of expedited transplantation in this population is further supported by the fact that liver transplantation within 30-days of listing is associated with reduced one-year post-transplant mortality. Additional research is therefore warranted regarding the timing of liver transplantation for patients with ACLF-3 with extra-hepatic organ failures.

In our analysis of post-transplant outcomes, we also identify the negative impact of mechanical ventilation at the time of liver transplantation on post-transplant mortality. It is difficult to compare these findings to prior multi-center studies, given the paucity of patients transplanted with ACLF-3 and respiratory failure. For instance, in the CANONIC study, no patient with respiratory failure underwent liver transplantation, suggesting that this was considered a contraindication for transplantation among the participating centers.[4] Additionally, analysis by Artru et al. showed that only seven of the 73 patients with ACLF-3 had respiratory failure.[3] However, a recent analysis of the UNOS database regarding the prevalence of organ failures among patients transplanted within 30 days from waitlist registration, did reveal that respiratory failure as determined by need for mechanical ventilation was associated with reduced post-transplant survival.[6] The authors concluded, however, that given overall post-liver transplantation survival among patients, the presence of respiratory failure should not be considered a contraindication to liver transplantation. There are important distinctions between this study and ours that have lead us to a different conclusion. Our analysis focused specifically on the ACLF-3 population rather than all transplant recipients, and as such we were able to identify factors associated with better or worse post-transplant survival, which impact this group. In this setting, we determined a 10% patient survival difference at one year depending on the presence or absence of mechanical ventilation at liver transplantation, with ability to only marginally improve patient survival with use of a higher quality organ or with transplantation within 30 days. In consideration of these findings, however, we suggest proceeding with caution when considering transplant for patients with ACLF-3 who are mechanically ventilated at the time of transplantation.

Data in the general population indeed suggests that increasing duration of mechanical ventilation is associated with an overall increased risk of mortality, due to infection, muscle deconditioning, and tracheal injury.[14,15] Based on our results, this general principle appears also to be applicable to the post-liver transplantation population.[16,17] One single-center study

regarding post-transplant outcomes demonstrated that intubated patients in the intensive care unit had a trend toward increased one-year mortality in the intubated ICU group.[17] The most common cause of death in this group within the first year was due to infections, including three patients with pneumonia. In a separate study of adult liver transplantation patients, those intubated for greater than four days had a higher rate of ventilator acquired pneumonia and a 30-day mortality rate of 32%.[16]

Traditionally, organs with a high DRI have been used for recipients with uncompetitive MELD scores (MELD score 10-14),[18] though subsequent data has also shown that the benefit of sub-optimal organs occurs as well in high MELD patients, suggesting that earlier transplantation of sicker recipients may supersede the need for an optimal organ.[19–21] Our analysis demonstrated that a high DRI is associated with increased one-year mortality. However, when compared to data regarding one-year survival probability without transplantation both in our study and from previous findings,[3–4] it is clear that liver transplantation offers a survival benefit regardless of organ quality. The concern for transplanting these patients lies with the possibility of transplanting a liver into a recipient who ultimately does not benefit. However, given the significantly greater survival amongst those receiving transplantation and the need to undergo liver transplantation rapidly, we do not argue against use of a marginal organ in the ACLF-3 population where one-year survival after liver transplantation remains above 80%, unless the patient is also mechanically ventilated at the time of transplant. It may be preferable to accept a marginal organ early after development of ACLF-3, rather than waiting for a better organ since we have demonstrated that outcomes decline with time. We suggest additional research regarding use of a high DRI liver after stabilization or improvement of organ failures, as this may represent a "window" whereby transplantation, even with a marginal organ, provides a life-saving intervention.

Our study also evaluated the prognostic utility of additional parameters to assess post-transplant survival beyond MELD score and organ failure, namely KPS and futility risk score.

Though frailty can be determined by a variety of measures, KPS is readily available in the UNOS database and has been previously assessed as a predictor of reduced post-transplant survival among those with functional status < 80%.[22] Though our study did not find KPS to be a predictor of mortality among patients with ACLF-3, we believe these findings are related to the low percentage of patients in this group with a high KPS score (2.0%). Further studies are therefore needed to determine whether frailty, as measured by KPS or other assessments, can provide additional information regarding post-liver transplantation outcomes for patients with ACLF-3. Our analysis of the futility risk score similarly was not associated with one-year post-transplant mortality.[9] We believe there are two potential reasons for this. First, this scoring system was validated for five-year patient survival, whereas we evaluated shorter-term outcomes. Secondly, the population analyzed was restricted to HCV negative recipients, while HCV comprised approximately 12% of our study population.

The UNOS registry has certain advantages for this investigation, particularly the availability of a large sample size of patients with ACLF-3 across multiple regions in the United States. However, several limitations exist regarding our analysis of this database, given the nature of retrospectively analyzing a large public database. We would like to discuss these limitations in detail. First, there is the potential for misclassification at listing and transplantation. In particular, there are several patients with renal failure who are categorized as no ACLF, since there is no documented decompensating event of ascites or hepatic encephalopathy. It is likely that many of these patients had compensated cirrhosis with chronic kidney disease, since they did not have ascites, which is a necessary component of hepatorenal syndrome. Nonetheless, it is also feasible that certain individuals classified as no ACLF had a decompensating event such as variceal bleeding or bacterial infection, which is not captured in the UNOS database. Similarly, misclassification may also occur regarding grade of HE, as this is reported based on the subjective assessment of the treating provider. Secondly, our analysis lacks information regarding infection rates. Therefore certain patients with ACLF precipitated by bacterial infection

may not have been identified. Additionally, infection is a cause of both waitlist and post-transplant mortality, which we were unable to account for. Our analysis was focused on one-year survival after liver transplantation as opposed to five-year survival, as we believed this metric to be more reflective of the post-transplant complications associated with ACLF, whereas longer-term outcomes may reflect sequelae related to chronic medical comorbidities. Regarding our Cox proportional hazards model, we identified variables a priori based on hypothesized clinical significance to utilize a manual backward selection method to build our final model. However, we acknowledge the potential for introduced bias that results from this method that may potentially lead to observed associations that do not exist or lack of associations when they truly exist (type 1 error). While we attempted to limit the potential for spurious associations by a priori focusing on variables that were clinically relevant, we acknowledge this inherent limitation when using such methods with large datasets. Finally, the study utilizes the presence of mechanical ventilation as an indicator for respiratory failure. However, the indication for mechanical ventilation is not available, and certain patients may have been ventilated for airway protection due to altered mental status, whereas other patients with significant lung injury that qualifies as respiratory failure may have not been intubated at the time of liver transplantation. However, despite these limitations, the findings from this analysis are important as they reveal distinct clinical characteristics of patients with ACLF who are less likely to survive on the waiting list or following liver transplantation, since we include a large number of patients with ACLF-3.

In conclusion, mortality or removal from the waiting list is highest among patients with ACLF-3 regardless of MELD score category, and nearly 44% of patients with ACLF-3 with a MELD score less than 25 will die or be removed within 28 days of listing. These findings suggest that such patients may benefit from additional priority for organ allocation, to enable liver transplantation within a shorter time frame. Liver transplantation for patients with ACLF-3 dramatically increases overall survival compared to supportive care, and transplantation within 30 days of listing improves post-transplant survival, further bolstering the benefit of earlier liver

transplantation for this population. The presence of mechanical ventilation at liver transplantation has the strongest association with reduced post-transplant survival, suggesting that caution should be exercised with transplantation of these individuals. Finally, although using better quality organs improves post liver transplantation survival, waiting for good quality organs needs to be balanced against risk of death on the waiting list.

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Figure 1. Cumulative incidence of mortality or removal from the waiting list

Figure 2a. Death or removal from the waiting list within 28 days, according to ACLF and MELD-Na category

Figure 2b. Death or removal from the waiting list within 90 days, according to ACLF and MELD-Na category

Figure 3a. One-year post-transplant patient survival according to presence of mechanical ventilation at LT, among ACLF-3 patients ($p<0.001$)

Figure 3b. One-year post-transplant patient survival comparing no ACLF, ACLF-1, ACLF-2 and ACLF-3 not mechanically ventilated at transplantation ($p<0.001$)

Figure 3c. One-year post-transplant patient survival among ACLF-3 patients mechanically ventilated at LT, stratified by DRI ($p<0.001$)

Figure 3d. One-year post-transplant patient survival among ACLF-3 patients mechanically ventilated at LT, stratified by transplantation within 30 days ($p<0.001$)

Table 1. Characteristics of study population, categorized by ACLF grade at the time of waitlist registration.

Characteristics	No ACLF (n=79,520)	ACLF-1 (n=9,640)	ACLF-2 (n=6,079)	ACLF-3 (n=5,355)	p-value*
Age, mean (SD)	53.8 (10.2)	54.1 (10.1)	51.1 (11.3)	51.8 (10.8)	<0.001
Male, n (%)	50,035 (62.9)	6,111 (63.9)	3,792 (62.4)	3,266 (60.9)	<0.001
Race, n (%)					<0.001
Caucasian	58,969 (74.9)	6,731 (70.7)	3,946 (65.8)	3,465 (65.1)	
African American	6,061 (7.8)	1,021 (10.7)	758 (12.7)	656 (12.4)	
Hispanic	11,098 (14.1)	1,514 (15.9)	999 (16.6)	909 (17.2)	
BMI, mean (SD)	28.5 (5.8)	28.5 (5.9)	29.2 (6.6)	29.7 (6.6)	0.092
Etiology, n (%)					<0.001
NASH	12,608 (22.8)	1,588 (22.9)	714 (19.2)	581 (17.2)	
HCV	20,989 (38.1)	2,087 (30.1)	1,026 (27.5)	1,014 (29.9)	
ALD	14,979 (27.2)	2,472 (35.7)	1,602 (43.8)	1,330 (39.3)	
HCV/ALD	6,528 (11.9)	786 (11.3)	387 (10.4)	460 (13.6)	
MELD score, mean (SD)	15.4 (5.5)	25.7 (5.0)	34.0 (5.3)	36.6 (4.9)	<0.001
MELD-Na score, mean (SD)	17.7 (6.1)	27.6 (5.0)	34.8 (4.9)	36.8 (4.7)	<0.001
Diabetes mellitus, n (%)	18,569 (24.2)	2,645 (28.6)	1,223 (20.9)	1,080 (21.3)	<0.001
Albumin (SD)	3.03 (0.6)	2.94 (0.8)	2.96 (0.8)	3.08 (0.8)	<0.001
Liver failure, n (%)	2,895 (3.6)	2,556 (26.5)	4,711 (77.6)	4,343 (81.2)	<0.001
Mechanical ventilation, n (%)	0 (0)	0 (0)	220 (3.6)	2,165 (40.4)	<0.001
Circulatory failure, n (%)	71 (0.1)	27 (0.3)	430 (7.1)	2,470 (46.1)	<0.001
Coagulation failure, n (%)	1,171 (1.5)	1,735 (18.1)	3,235 (53.2)	3,410 (63.7)	<0.001
Neurologic failure, n (%)	4,003 (4.8)	347 (3.6)	1,641 (26.9)	2,457 (56.0)	<0.001
Renal failure, n (%)	4,327 (5.4)	5,322 (55.3)	3,562 (58.6)	4,322 (80.7)	<0.001

* Evaluation of differences across all ACLF categories using ANOVA and Chi-square testing

Table 2. Recipient and donor characteristics at the time of liver transplantation, categorized by ACLF grade.

Recipient characteristics	**No ACLF (n=29,283)**	**ACLF-1 (n=7,375)**	**ACLF-2 (n=7,513)**	**ACLF-3 (n=6,381)**	**p-value***
Age, mean (SD)	54.2 (10.4)	54.1 (9.9)	52.3 (10.7)	52.7(10.5)	<0.001
Male, n (%)	19,368 (66.1)	4,829 (65.5)	4,740 (63.1)	4,007 (62.8)	<0.001
Race, n (%)					<0.001
Caucasian	22,479 (77.5)	5,434 (74.5)	5,123 (67.6)	4,155 (65.9)	
African American	2,505 (8.6)	715 (9.8)	858 (11.5)	665 (10.6)	
Hispanic	3,157 (10.9)	957 (13.1)	1,173 (15.8)	1,202 (19.1)	
BMI, mean (SD)	28.1 (5.7)	28.2 (5.8)	28.4 (6.2)	28.8 (6.4)	
Etiology, n (%)					<0.001
NASH	3,906 (20.8)	1,120 (21.9)	897 (18.9)	740 (17.8)	
HCV	7,711 (41.1)	1,711 (33.6)	1,593 (33.7)	1,406 (33.7)	
ALD	4,811 (25.7)	1,669 (32.6)	1,658 (35.1)	1,449 (34.9)	
HCV/ALD	2,330 (12.4)	601 (11.8)	580 (12.3)	554 (13.4)	
MELD score, mean (SD)	17.7 (5.9)	27.1 (4.7)	33.3 (5.4)	37.3 (4.2)	
MELD-Na score, mean (SD)	20.0 (6.5)	28.8 (4.5)	34.2 (4.9)	37.4 (4.1)	<0.001
Diabetes mellitus, n (%)	6,543 (23.2)	1,941 (27.5)	1,609 (22.2)	1,358 (22.2)	<0.001
Albumin, mean (SD)	2.96 (0.7)	2.95 (0.8)	3.0 (0.8)	3.2 (0.9)	<0.001
Karnofsky performance status >=80%	7,798 (27.4)	1,041 (14.5)	548 (7.5)	155 (2.5)	<0.001
Liver failure, n (%)	1,529 (5.2)	1,935 (26.3)	4,884 (65.1)	1,045 (16.4)	<0.001
Mechanical ventilation, n (%)	0 (0)	0 (0)	177 (2.4)	2,294 (35.9)	<0.001
Circulatory failure, n (%)	54 (0.2)	39 (0.5)	554 (7.4)	3,252 (51.1)	<0.001
Coagulation failure, n (%)	849 (2.9)	1,690 (22.9)	3,625 (48.3)	4,060 (63.6)	<0.001
Neurologic failure, n (%)	1,416 (4.8)	0 (0)	1,441 (19.2)	3,101 (48.6)	<0.001
Renal failure, n (%)	2,025 (6.9)	3,711 (50.3)	4,345 (57.9)	5,346 (83.8)	<0.001
Number of organ failures (n,%):					
Three				3,583 (56.2)	
Four				1,646 (25.9)	
Five				866 (13.6)	
Six				286 (4.5)	
Days from listing to LT (median, IQR)	106 (32-291)	48 (12-175)	23 (7-120)	12 (4-62)	<0.001
Donor characteristics					
Age, mean (SD)	41.5 (16.8)	39.9 (16.1)	39.2 (15.6)	38.7 (15.2)	<0.001
Deceased donor	27,336 (93.5)	7,270 (98.6)	7,483 (99.6)	6,378 (99.9)	<0.001
Male, n (%)	17,345 (59.3)	4,345 (58.9)	4,497 (59.9)	3,866 (60.6)	0.022
Diabetes mellitus, n (%)	3,186 (11.5)	673 (9.2)	689 (9.2)	562 (8.8)	<0.001
Normal coronary angiogram, n (%)	2,716 (70.7)	812 (69.8)	952 (74.1)	869 (73.0)	0.074
Donor race, n (%)					<0.001

Caucasian	19,998 (68.3)	5,035 (68.3)	4,788 (63.7)	3,999 (62.7)	
African American	5,254 (17.9)	1,228 (16.7)	1,223 (16.3)	959 (15.0)	
Hispanic	3,007 (10.2)	855 (11.6)	1,196 (15.9)	1,146 (17.9)	
Cause of death, n (%)					0.001
Anoxia	6,722 (24.6)	1,766 (24.3)	1,936 (25.9)	1,542 (24.1)	
CVA/Stroke	10,532 (38.4)	2,663 (36.6)	2,648 (35.4)	2,271 (35.6)	
Head trauma	9,357 (34.2)	2,641 (36.3)	2,708 (36.2)	2,425 (38.0)	
CNS tumor	137 (0.5)	36 (0.5)	30 (0.4)	24 (0.4)	
Donor risk index >= 1.7	9,808 (33.5)	1,880 (25.5)	1,822 (24.3)	1,464 (22.9)	<0.001

* Evaluation of differences across all ACLF categories using ANOVA and Chi-square testing

Table 3. Comparison of recipient and donor characteristics of transplanted ACLF-3 patients, grouped by 1-year post-transplant survival.

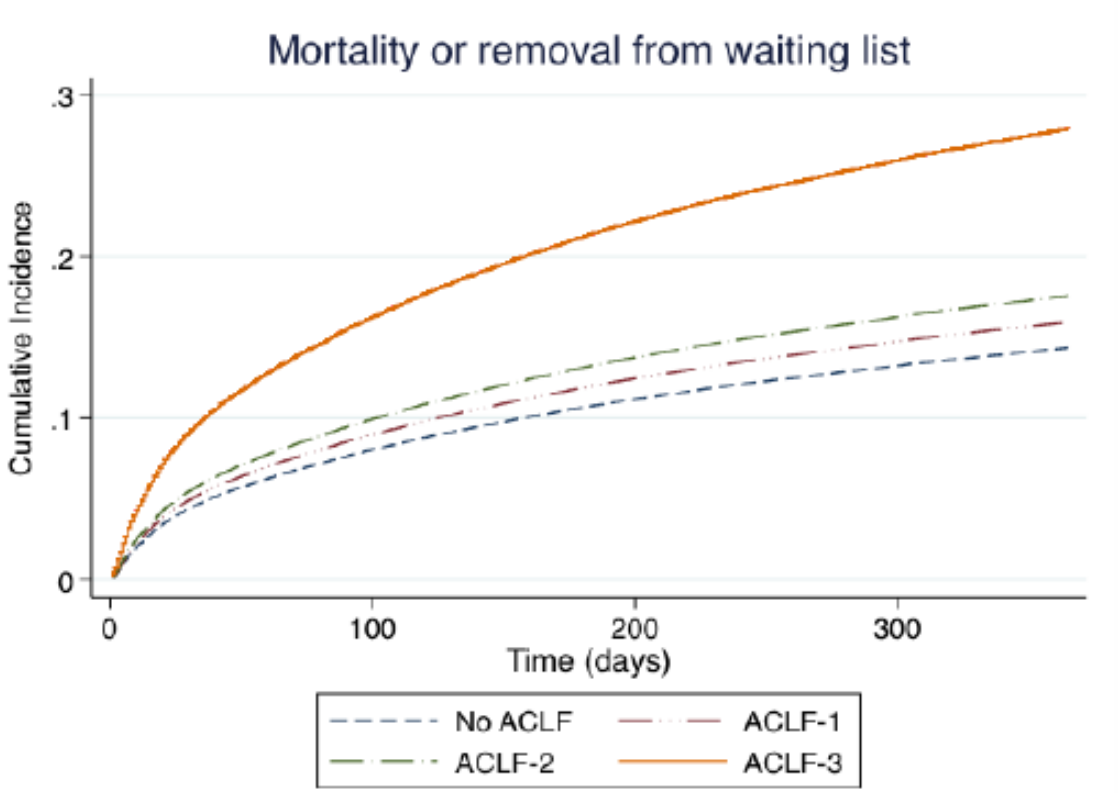
	Mortality at 1 year (n=1,157)	Survival at 1 year (n=5,224)	p-value*
Age, mean (SD)	52.9 (10.6)	51.7 (10.6)	<0.001
Male, n (%)	723 (62.5)	3,284 (62.8)	0.445
Race, n (%)			0.224
Caucasian	800 (70.2)	3,355 (64.9)	
African American	119 (10.5)	546 (10.6)	
Hispanic	180 (15.8)	1,022 (19.8)	
MELD score, mean (SD)	36.8 (4.7)	37.4 (4.1)	0.221
MELD-Na, mean (SD)	36.8 (4.7)	37.5 (4.0)	0.214
Etiology, n (%)			<0.001
NASH	129 (18.0)	611 (17.8)	
HCV	299 (41.8)	1,107 (32.3)	
ALD	195 (27.3)	1,254 (36.5)	
Karnofsky performance status >= 80%, n (%)	17 (1.5)	138 (2.7)	0.020
Futility risk index > 8, n (%)	433 (37.4)	1,287 (24.6)	<0.001
Donor risk index >= 1.7, n (%)	320 (27.7)	1,144 (21.0)	<0.001
Transplantation within 30 days of listing, n (%)	642 (55.4)	3,112 (59.5)	0.013
Mechanical ventilation, n (%)	567 (49.0)	1,727 (33.1)	<0.001
Renal failure, n (%)	964 (83.4)	4,382 (83.9)	0.716
Circulatory failure, n (%)	701 (60.6)	2,551 (49.8)	<0.001
Liver failure, n (%)	944 (81.9)	4,383 (83.9)	0.094
Neurologic failure, n (%)	1,085 (47.6)	2,015 (49.1)	0.136
Coagulation failure, n (%)	631 (54.5)	3,429 (65.6)	<0.001
Organ failures:			
Three, n (%)	571 (49.3)	3,012 (57.7)	<0.001
Four or more, n (%)	586 (50.7)	2,212 (42.3)	<0.001

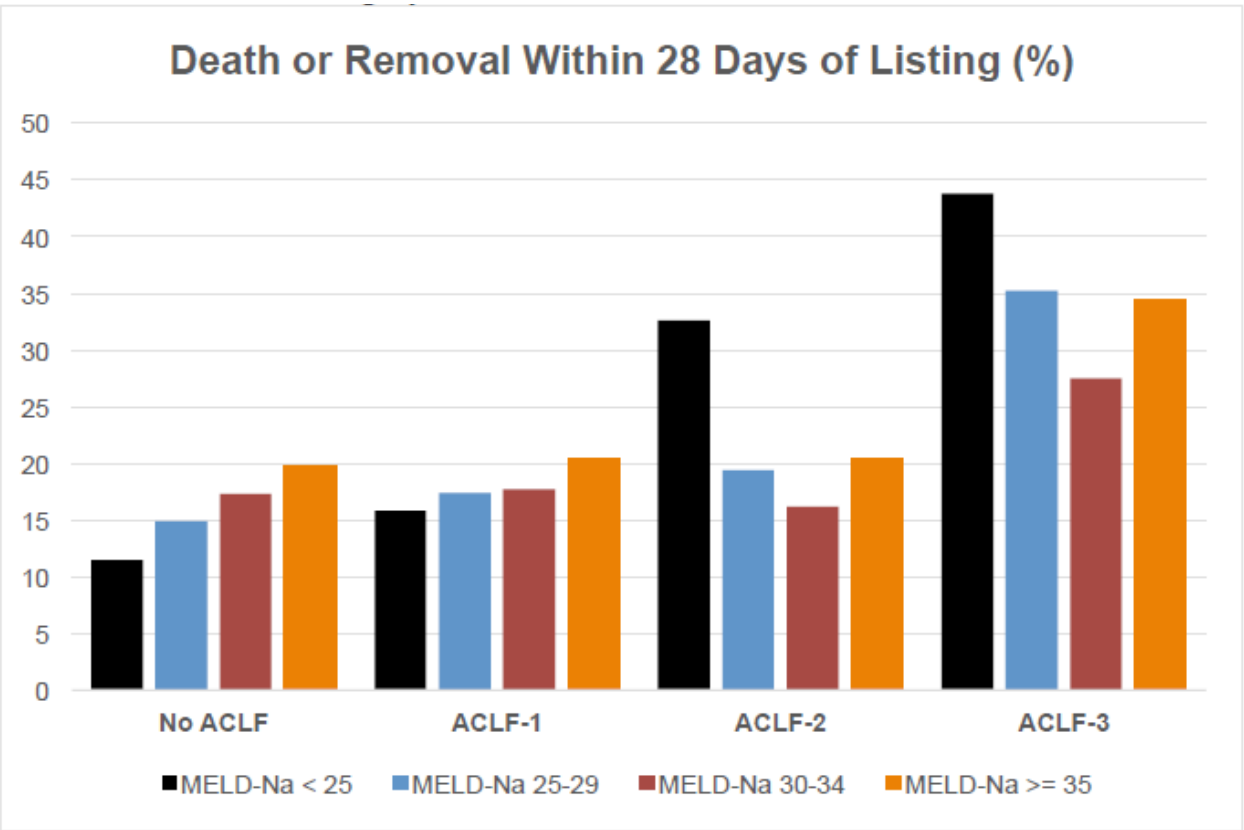
* Evaluation of differences between those who survived and died at one year post LT

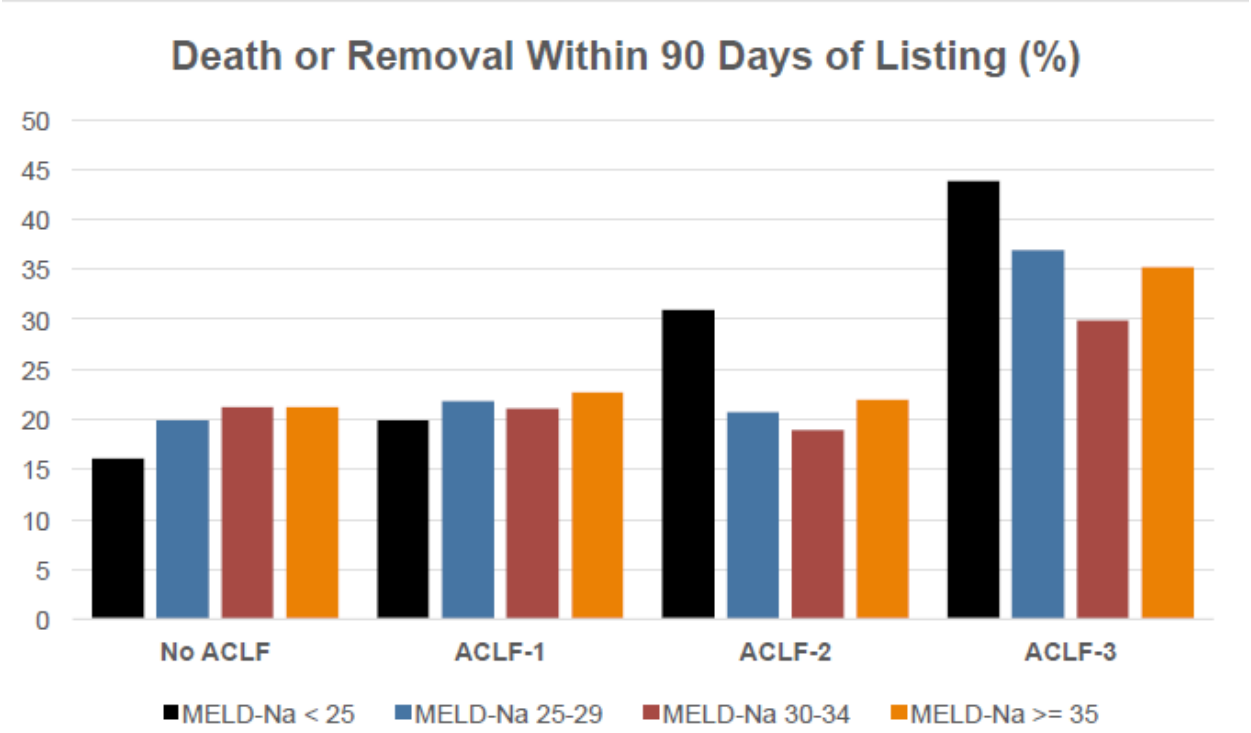
Table 4. Univariable and multivariable Cox proportional hazards regression evaluating risk factors for one-year post-transplant mortality among ACLF-3 patients.

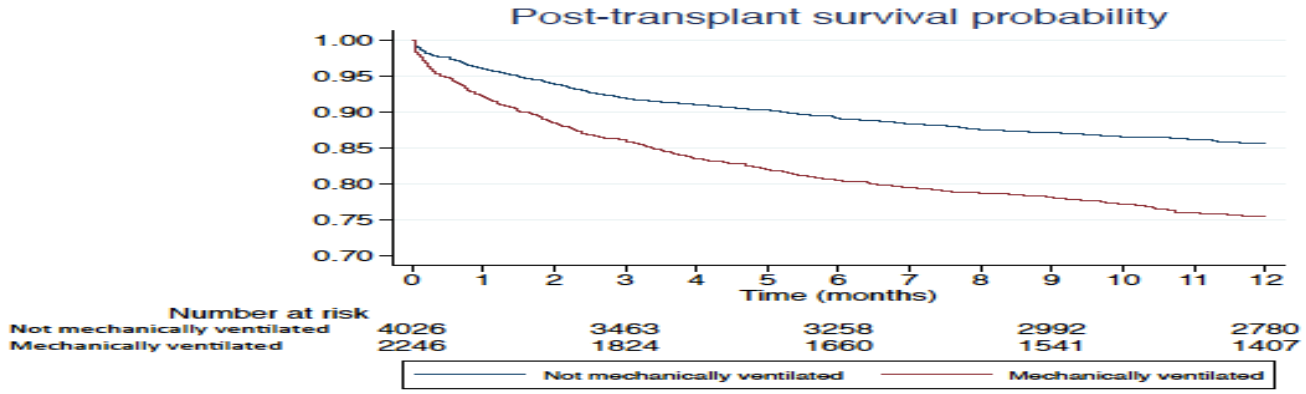
	Univariable analysis HR (95% CI)	**Multivariable analysis* HR (95% CI)**
Functional status >= 80%	0.65 (0.47-0.89)	0.76 (0.55-1.06)
Futility score > 8 points	1.57 (1.42-1.74)	1.12 (0.97-1.30)
Donor risk index >= 1.7	1.25 (1.12-1.40)	1.22 (1.09-1.35)
Transplant within 30 days of listing	0.87 (0.79-0.96)	0.89 (0.81-0.98)
Mechanical ventilation	1.56 (1.42-1.72)	1.49 (1.22-1.84)
Circulatory failure	1.37 (1.24-1.51)	0.90 (0.78-1.05)
4 or more organ failures	1.28 (1.16-1.41)	1.04 (0.92-1.19)

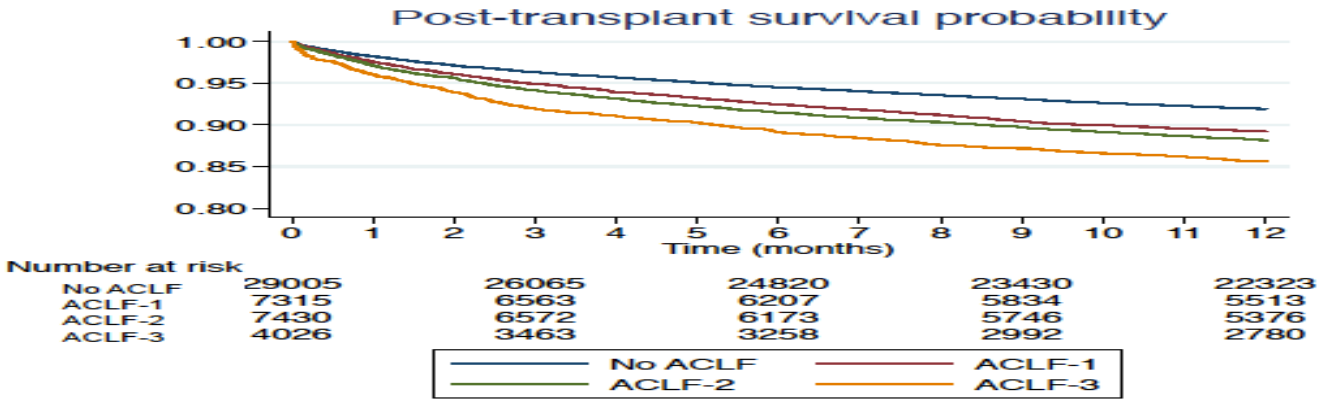
*adjusted for age and MELD-Na score

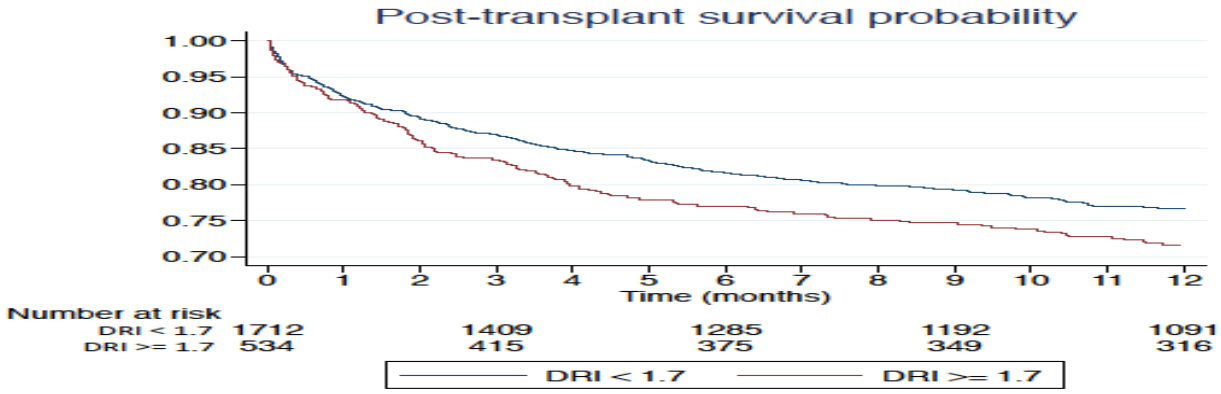



Death or Removal Within 28 Days of Listing (%)
50
45
40
35
30
25
20
15
10
5
0
No ACLF
ACLF-1
ACLF-2
ACLF-3
MELD-Na < 25
MELD-Na 25-29
MELD-Na 30-34
MELD-Na >= 35


Death or Removal Within 90 Days of Listing (%)
50
45
40
35
30
25
20
15
10
5
0
No ACLF
ACLF-1
ACLF-2
ACLF-3
MELD-Na < 25
MELD-Na 25-29
MELD-Na 30-34
MELD-Na >= 35


Post-transplant survival probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (months)
Number at risk
Not mechanically ventilated 4026 3463 3258 2992 2780
Mechanically ventilated 2246 1824 1660 1541 1407
Not mechanically ventilated
Mechanically ventilated


Post-transplant survival probability
1.00
0.95
0.90
0.85
0.80
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (months)
Number at risk
No ACLF 29005 26065 24820 23430 22323
ACLF-1 7315 6563 6207 5834 5513
ACLF-2 7430 6572 6173 5746 5376
ACLF-3 4026 3463 3258 2992 2780
No ACLF
ACLF-1
ACLF-2
ACLF-3


Post-transplant survival probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (months)
Number at risk
DRI < 1.7 1712 1409 1285 1192 1091
DRI >= 1.7 534 415 375 349 316
DRI < 1.7
DRI >= 1.7

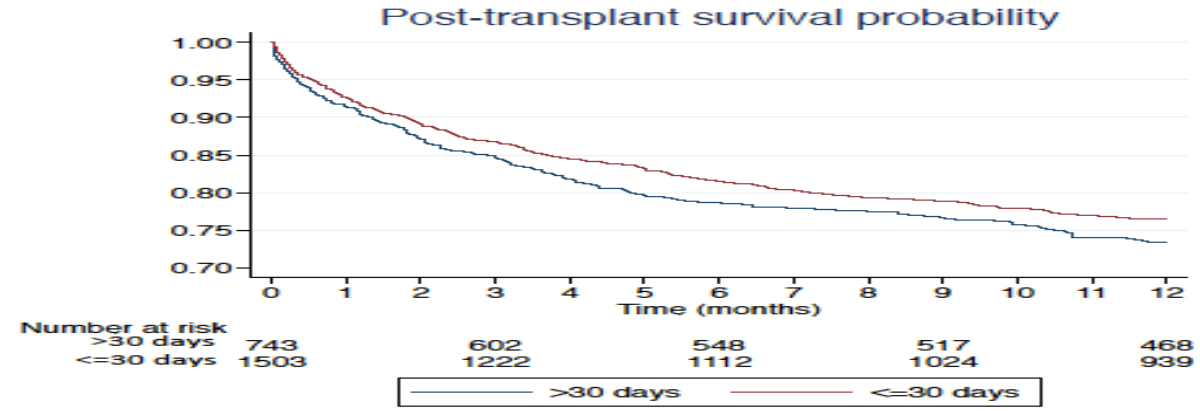

Post-transplant survival probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (months)
Number at risk
>30 days 743 602 548 517 468
<=30 days 1503 1222 1112 1024 939
>30 days
<=30 days

Table S1. Criteria to determine presence of organ dysfunction/failure

Organ failure	UNOS database variables
Liver	Total bilirubin > 12 mg/dL
Renal	Insufficiency: creatinine 1.5-1.9 mg/dL Failure: creatinine > 2.0 mg/dL or renal replacement therapy
Coagulation	INR > 2.5
Neurologic	grade 3-4 encephalopathy
Circulatory	requirement of vasopressors
Respiratory	requirement of mechanical ventilation

Table S2. Death or wait-list removal within 28 and 90 days of transplant listing, among MELD, MELD-Na and ACLF categories

	No ACLF **n, (%)**	**ACLF-1** **n, (%)**	**ACLF-2** **n, (%)**	**ACLF-3** **n, (%)**
MELD < 25				
28 days	857 (12.4)	161 (17.3)	33 (30.6)*	44 (43.4)*
90 days	3,065 (17.2)	421 (22.3)	47 (27.9)*	56 (43.8)*
MELD-Na < 25				
28 days	579 (11.5)	71 (15.8)	30 (32.6)*	49 (43.8)*
90 days	2243 (16.1)	192 (19.9)	43 (30.9)*	60 (43.8)*
MELD 25-29				
28 days	278 (15.4)	297 (17.3)	75 (17.7)	93 (32.6)
90 days	508 (18.6)	535 (20.7)	117 (19.6)	118 (34.2)
MELD-Na 25-29				
28 days	422 (14.9)	240 (17.4)	42 (19.4)	80 (35.2)
90 days	1,065 (19.9)	505 (21.8)	62 (20.7)	101 (36.9)
MELD 30-34				
28 days	145 (18.6)	234 (18.1)	249 (17.4)	182 (28.3)
90 days	213 (21.5)	334 (20.6)	339 (19.5)	224 (30.6)
MELD-Na 30-34				
28 days	256 (17.3)	335 (17.7)	210 (16.2)	166 (27.5)
90 days	445 (21.2)	534 (21.1)	310 (18.9)	210 (29.9)

MELD >=35				
28 days	43 (20.3)	72 (20.4)	564 (20.3)	1,314 (34.6)
90 days	52 (21.3)	97 (23.2)	681 (22.3)	1,409 (35.3)
MELD-Na >=35				
28 days	66 (19.8)	118 (20.5)	639 (20.4)	1,341 (34.5)
90 days	85 (21.2)	156 (22.7)	769 (22.0)	1,436 (35.2)

* Chi-square comparison to no ACLF and ACLF-1 groups with MELD or MELD-Na score >= 35 ($p<0.001$)

Table S3. Post-transplant patient survival by ACLF category

	Patient survivor function (95% CI)			
	30 days	**90 days**	**180 days**	**365 days**
No ACLF	0.982 (0.980-0.984)	0.963 (0.961-0.965)	0.945 (0.942-0.947)	0.919 (0.915-0.921)
ACLF-1	0.975 (0.971-0.978)	0.949 (0.944-0.954)	0.925 (0.919-0.931)	0.891 (0.883-0.898)
ACLF-2	0.971 (0.966-0.975)	0.942 (0.936-0.947)	0.915 (0.908-0.922)	0.881 (0.873-0.888)
ACLF-3	0.946 (0.940-0.951)	0.898 (0.890-0.901)	0.861 (0.851-0.869)	0.818 (0.808-0.827)

Table S4. One year post-liver transplant survival probability among patients with ACLF3

Variable	Yes	No	p-value
Lack of mechanical ventilation	0.854 (0.842-0.850)	0.753 (0.735-0.771)	<0.001
Lack of circulatory failure	0.853 (0.839-0.865)	0.784 (0.68-0.798)	<0.001
Three organ failure only	0.839 (0.826-0.851)	0.791 (0.775-0.806)	<0.001
Karnofsky performance status >=80%	0.885 (0.821-0.927)	0.818 (0.807-0.827)	0.008
DRI < 1.7	0.829 (0.817-0.839)	0.781 (0.758-0.803)	<0.001
Futility score <8	0.844 (0.833-0.854)	0.747 (0.724-0.768)	<0.001
Transplantation within 30 days of listing	0.825 (0.813-0.837)	0.794 (0.786-0.821)	0.007
DRI < 1.7 among patients with respiratory failure	0.765 (0.743-0.785)	0.716 (0.674-0.754)	0.034
Transplantation within 30 days of listing with respiratory failure	0.765 (0.742-0.786)	0.733 (0.698 -0.764)	0.032

Table S5. Prevalence of specific organ failures at waitlist registration among patients with ACLF-2, stratified by mortality or survival within 90 days of listing

	Waitlist mortality or removal (n=1,184)	Waitlist survival or transplantation (n=4,895)	p-value
Renal failure	731 (61.7)	2,831 (57.8)	0.014
Circulatory failure	84 (8.1)	346 (7.1)	0.975
Mechanical ventilation	51 (4.3)	169 (3.5)	0.158
Neurologic failure	373 (31.5)	1,268 (25.9)	<0.001
Coagulation failure	573 (48.4)	2,662 (54.4)	<0.001
Liver failure	929 (78.6)	3,782 (77.3)	0.353

Table S6. Prevalence of specific organ failures at LT among patients with ACLF-2, stratified by mortality or survival within 1-year post-transplant

	Mortality (n=908)	Survival (n=6,884)	p-value
Renal failure	574 (65.3)	3,771 (56.9)	<0.001
Circulatory failure	90 (11.1)	456 (6.9)	<0.001
Mechanical ventilation	45 (5.6)	129 (1.9)	<0.001
Neurologic failure	181 (20.6)	1,260 (19.0)	0.266
Coagulation failure	355 (40.3)	3,270 (49.3)	<0.001
Liver failure	504 (57.3)	4,380 (66.1)	<0.001

Table S7. Univariable and multivariable Cox proportional hazards regression regarding one-year post-transplant mortality among ACLF-3 patients.

	Univariable analysis **HR (95% CI)**	**Multivariable analysis*** **HR (95% CI)**
Renal failure	1.25 (1.13-1.41)	1.38 (1.19-1.60)
Mechanical ventilation	2.07 (1.67-2.57)	2.01 (1.46-2.76)
Circulatory failure	1.62 (1.39-1.90)	1.31 (1.04-1.64)
Neurologic failure	1.22 (1.08-1.37)	1.09 (0.99-1.19)
Coagulation failure	0.71 (0.65-0.79)	1.03 (0.88-1.21)
Liver failure	0.68 (0.61-0.76)	0.98 (0.85-1.11)

*adjusted for age and MELD-Na score

Table S8. Death or wait-list removal within 90 days of transplant listing, among meld, MELD-Na and ACLF categories after removal of transplanted patients

	No ACLF	**ACLF-1**	**ACLF-2**	**ACLF-3**
MELD-Na < 25	2,243 (16.5)	192 (21.5)	43 (34.7)	60 (61.2)
MELD < 25	3,065 (17.5)	421 (21.9)	47 (33.3)	56 (61.5)
MELD-Na 25-29	1,065 (21.4)	505 (39.9)	62 (49.2)	101 (75.9)
MELD 25-29	565 (29.2)	535 (48.6)	117 (54.7)	118 (71.5)
MELD-Na 30-34	445 (54.3)	534 (62.3)	310 (61.4)	210 (72.7)
MELD 30-34	167 (52.2)	334 (66.7)	339 (64.6)	224 (74.9)
MELD-Na >=35	85 (61.6)	156 (76.1)	769 (78.7)	1,436 (91.3)
MELD >=35	26 (70.2)	97 (78.9)	681 (79.9)	1,409 (91.7)

Figure S1. Patient survival after liver transplant according to ACLF category (p<0.001)

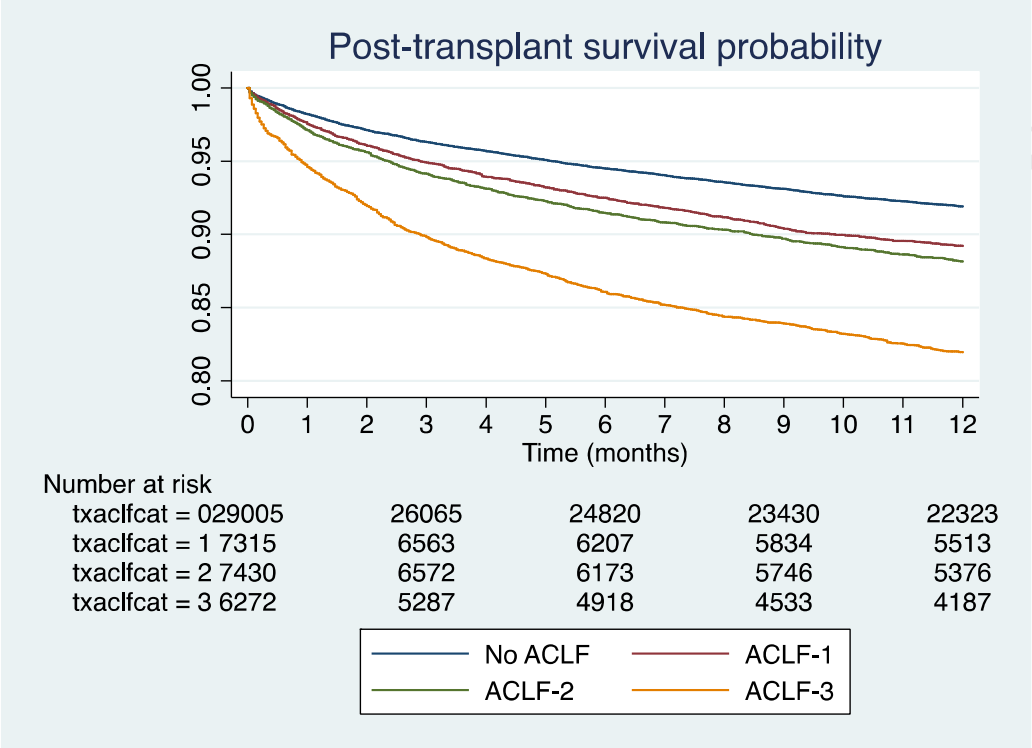


Figure S2. One-year patient survival after liver transplant according to futility score among ACLF3 patients (p<0.001)

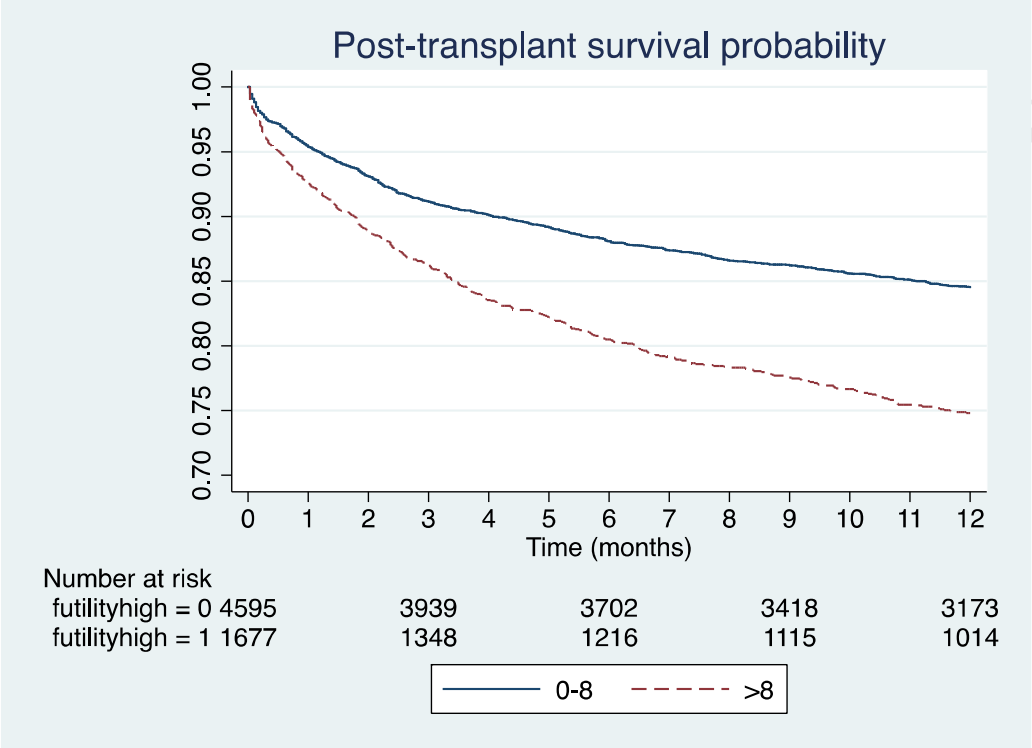


Figure S3. One-year patient survival after liver transplant according to donor risk index among ACLF3 patients (p<0.001)

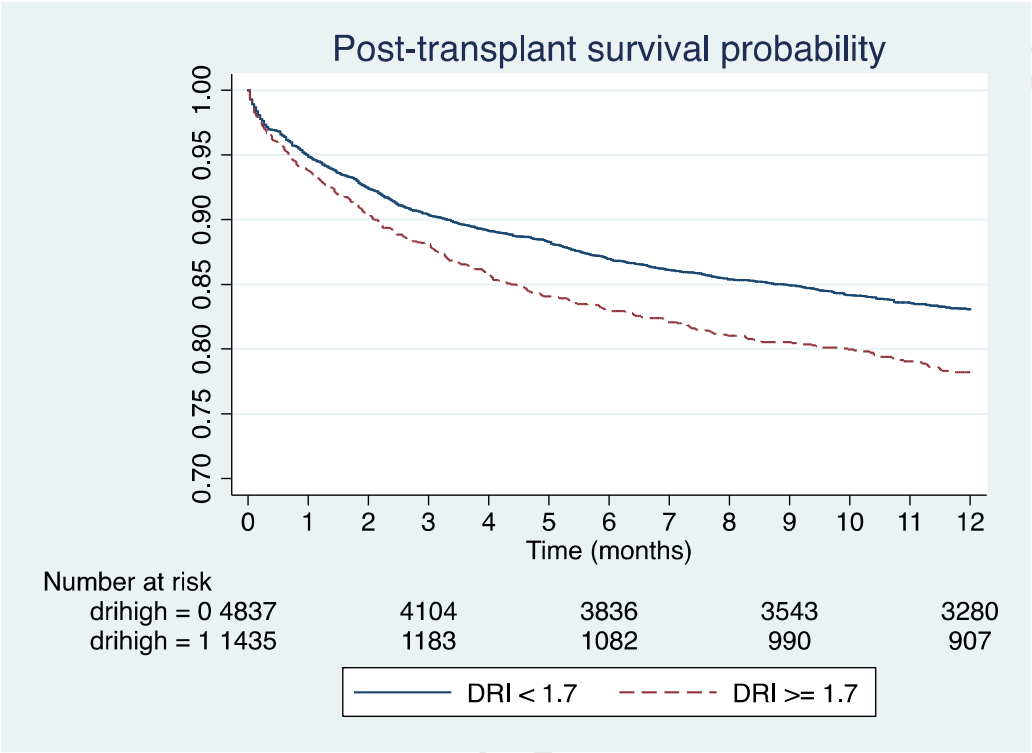


Figure S4. One-year patient survival after liver transplant according to presence of circulatory failure among ACLF3 patients (p<0.001)

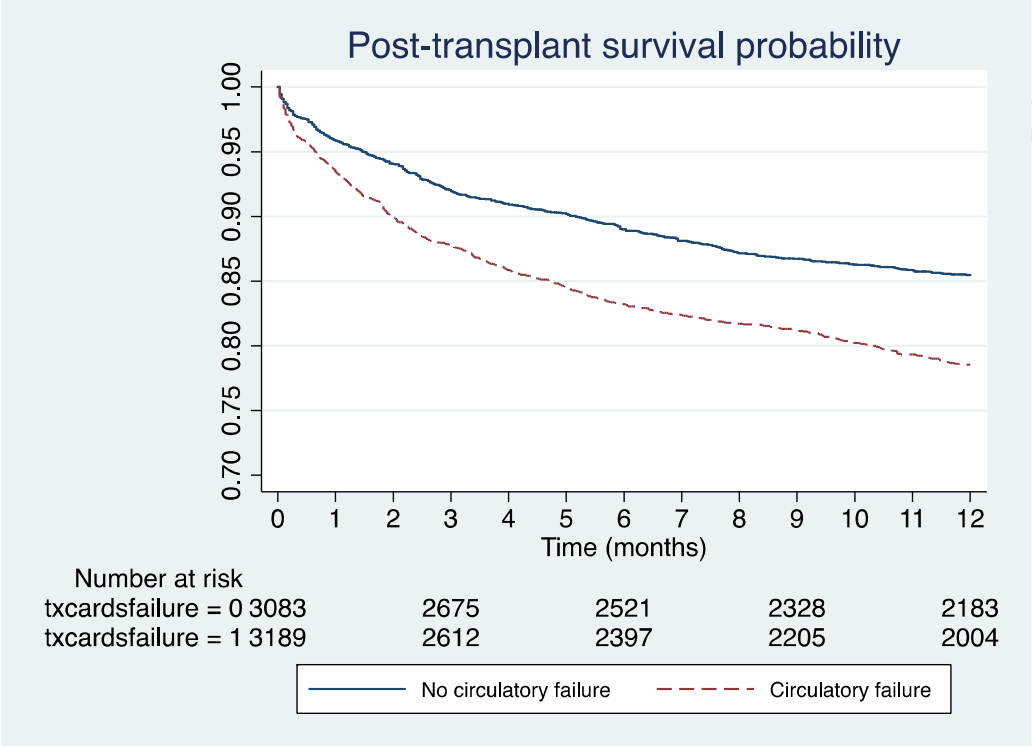


Figure S5. One-year patient survival after liver transplant according to transplantation within 30 days of waitlist registration, among ACLF3 patients (p=0.007)