Patients with acute on chronic liver failure grade three have greater 14-day waitlist mortality than status-1a patients

Journal:	*Hepatology*
Manuscript ID	HEP-19-0097.R1
Wiley - Manuscript type:	Original
Date Submitted by the Author:	26-Feb-2019
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Keywords:	cirrhosis, liver transplantation, portal hypertension, organ allocation, MELD score

Title: Patients with acute on chronic liver failure grade three have greater 14-day waitlist mortality than status-1a patients

Short Title: Waiting list mortality of ACLF-3 compared with status-1a

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Keywords: UNOS database; cirrhosis; MELD score; liver transplantation

Footnote page

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List of Abbreviations:

Liver transplantation (LT)

End-stage liver disease (ESLD)

Acute liver failure (ALF)

Acute on chronic liver failure grade three (ACLF-3)

Model for end-stage liver disease (MELD)

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

Grant Support:

None

Disclosures:

The authors have nothing to disclose regarding conflicts of interest relevant to this manuscript. Rajiv Jalan has research collaborations with Yaqrit, Thoeris, and Takeda. Rajiv Jalan is the inventor of MNK-6105/6106, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit limited, a spin out company from University College London.

Writing Assistance:

None

Author Contributions:

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Acquisition of data, analysis, and interpretation of data: VS, RW

Drafting of manuscript: VS, PS

Critical revision of manuscript for important intellectual content: VS, RW, RJ, CK, NM, AK, BF

Statistical analysis: VS, RW

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Abstract

Patients listed for liver transplantation (LT) as status-1a currently receive the highest priority on the waiting list. The presence of acute on chronic liver failure with three or more organs failing (ACLF-3) portends low survival without transplantation, which may not be reflected by the model for end-stage liver disease-sodium (MELD-Na) score. We compared short-term waitlist mortality for patients listed status-1a and those with ACLF-3 at listing. Data was analyzed from the United Network for Organ Sharing (UNOS) database, years 2002-2014 for 3,377 patients listed status-1a and 5,099 patients with ACLF-3. Candidates with ACLF were identified based on the EASL-CLIF criteria. MELD-Na score was treated as a categorical variable of scores <36, between 36-40 and >40. We used competing risks regression to assess waitlist mortality risk. Evaluation of outcomes through 21 days after listing demonstrated a rising trend in mortality among ACLF-3 patients at 7 days (18.0%), 14 days (27.7%) and 21 days (32.7%) (p<0.001), compared to a stable trend in mortality among individuals listed as status-1a at 7 days (17.9%), 14 days (19.3%) and 21 days (19.8%), (p=0.709). Multivariable modeling with adjustment for MELD-Na category revealed that patients with ACLF-3 had significantly greater mortality (SHR=1.45, 95% CI 1.31-1.61) within 14 days of listing compared to status-1a candidates. Analysis of the interaction between MELD-Na category and ACLF-3 showed patients with ACLF-3 had greater risk of 14-day mortality than status-1a listed patients, across all three MELD-Na categories.

Conclusion: Patients with ACLF-3 at the time of listing have greater 14-day mortality than those listed as status-1a, independent of MELD-Na score. These findings illustrate the importance of early transplant evaluation and consideration of transplant priority for patients with ACLF-3.

Introduction

Current organ allocation policy gives highest priority for liver transplantation (LT) to patients listed as status-1a(1), the majority of whom have acute liver failure (ALF), since these patients are considered to be at greatest risk of short-term mortality without transplant. A previous study by Sharma et al, however, demonstrated that patients with end-stage liver disease (ESLD) and a model for end-stage liver disease (MELD) score above 40 have a nearly two-fold greater risk of waitlist mortality within 14 days of listing compared to those listed as status-1a, while those with MELD scores of 36-40 had similar mortality and candidates with scores less than 36 had lower 14-day mortality.(2) The authors subsequently concluded that candidates with a MELD score above 40 should be assigned similar transplant priority to patients listed as status-1a. These findings were later validated in separate study, which analyzed a larger number of patients over a greater number of years.(3)

Acute on chronic liver failure (ACLF) is a syndrome characterized by acute hepatic decompensation, organ failures, and 28-day mortality of greater than 15%.(4) ACLF grade 3 (ACLF-3), defined as the development of three or more organ failures,(4) has an associated mortality without liver transplantation approaching 80% at 28-days and greater than 90% at one year.(5-7) Liver transplantation (LT) priority for patients with ACLF is currently guided by the model for end-stage liver disease-sodium (MELD-Na) scoring system. Although the MELD-Na score has been well validated for assessing prognosis in decompensated cirrhosis, ACLF represents a distinct clinical presentation, characterized by increased systemic inflammation and the development of extra-hepatic organ failures.(6, 8-10) Therefore, the mortality associated with ACLF, particularly at higher grades, may not be fully reflected in the MELD-Na score. Subsequently, our recent findings have demonstrated that patients listed for LT with ACLF-3 and a MELD-Na score less than 25, have greater waitlist mortality than those without ACLF and a MELD-Na score above 35.(11)

Given the markedly poor prognosis of ACLF-3, which may not be fully accounted for by the MELD or MELD-Na score, we sought to compare waitlist mortality between patients listed as status-1a and those with ACLF-3 at the time of listing, to determine whether ACLF-3 patients have comparable or worse waitlist survival relative to candidates listed status-1a. We hypothesized that the 14-day mortality among candidates with ACLF-3 would be greater than among individuals listed as status-1a, and this association would be independent of MELD-Na since patients with ACLF-3 may have multiple organ failures not captured by MELD-Na score. Such findings would underscore the importance of early recognition and transplant evaluation for patients with ACLF-3, along with consideration of additional priority on the waitlist for these patients.

Experimental Procedures

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.(12)

United Network for Organ Sharing (UNOS) database analysis

From the UNOS registry, we evaluated patients age 18 or older listed for liver transplantation from 2002 to 2014. Patients who had hepatocellular carcinoma (HCC) or received a MELD exception at the time of waitlist registration were excluded, as their assigned MELD or MELD-Na score may not reflect their laboratory score. Additionally, we excluded patients who were re-transplanted since the etiology of their organ dysfunction would likely be secondary to post-transplant complications as opposed to ESLD. We collected data regarding patient characteristics at the time of waitlist registration and outcomes before and after transplantation. Regarding etiology of liver disease, we examined the prevalence of the most common causes of liver disease in the United States, specifically hepatitis C virus (HCV), alcoholic liver disease (ALD), and non-alcoholic steatohepatitis (NASH). Patients were considered as having NASH as their primary etiology of cirrhosis if they were either diagnosed with NASH or cryptogenic cirrhosis with a concurrent diagnosis of diabetes mellitus or a body mass index above 30 kg/m^2.(13)

Identification of patients

Patients were categorized as status-1a listing, based on coding for the UNOS variable "init_stat.". Status-1a candidates were categorized as having acetaminophen toxicity if their primary or secondary diagnosis data field contained any of the following text: Tylenol, acetaminophen, Darvocet, Vicodin, or Percocet. ACLF-3 at the time of waitlist registration was identified based on the EASL-CLIF criteria of having a single hepatic decompensation such as

ascites, hepatic encephalopathy, variceal bleed, or bacterial infection and the presence of three or more 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.(4) (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(4) for coagulopathy, liver failure, renal dysfunction and renal failure, neurologic failure, and circulatory failure. We used mechanical ventilation as a surrogate marker for respiratory failure.

Outcomes

Our primary outcome was 14-day waitlist mortality, which we compared between patients listed as status-1a and those identified as having ACLF-3. This time point of 14 days was chosen for several reasons. First, the majority of patients listed status-1a for ALF will be transplanted or die within 14 days of listing.(14) As such, current UNOS policy specifies that requests for status-1a listing beyond 14 days result in a review of all status 1A or 1B liver candidate registrations within the donation service area at the transplant hospital.(1) Additionally, the prior study by Sharma et al utilized 14 days from waitlist registration as their primary outcome.(2) **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.(15) To determine if this outcome was met, patients needed to have one of the following outcomes: death, removal for medical unsuitability, or removal due to condition deteriorating/too sick for transplant.

For our assessment of patients post-liver transplantation, the primary outcome was patient survival at one-year. Although our waitlist analysis included all patients listed status-1a,

the post-transplant analysis only compared the survival probability of ALF and ACLF-3, since patients who were re-transplanted were excluded from our study.

Statistical analysis

Comparisons were made utilizing Chi-square testing for categorical variables and Student's t-test or Wilcoxon rank-sum testing for continuous variables between two groups, and analysis of variance with Bonferonni correction for three groups. Tests of trend were evaluated using Wilcoxon-type test for trend.(16) Waitlist mortality or removal was additionally compared using Fine and Gray competing risks regression using LT as the competing event, with creation of a cumulative incidence function. Differences between cumulative incidence functions were determined using Gray's test. We also utilized Fine and Gray multivariable competing risks regression univariable and multivariable modeling to assess the strength of association between status-1a listing, ACLF-3 and waitlist mortality. Independent variables incorporated into the multivariable models were selected a priori, based on hypothesized clinical significance. We chose to select variables a priori, due to the possibility of type 1 error when choosing variables using manual backwards selection. MELD and MELD-Na score was categorized as less than 36, 36-40 and greater than 40, as based on the previous findings from Sharma et al.(2) Goodness of fit was determined using Cox-Snell residuals. For our post-transplant analysis, we compared one-year survival probability after LT between those listed as status-1a and patients with ACLF-3 using Kaplan-Meier methods, with differences in survival probabilities assessed by log-rank testing. All statistical analyses were performed using the Stata statistical package (version 14, Stata Corporations, TX).

Results

Study population characteristics

Table 1 describes the study population at waitlist registration. We excluded 14,585 patients under 18 years of age, 24,867 patients with HCC, 12,804 patients who received non-HCC exceptions, and 3,017 patients who underwent repeat transplantation. A total of 8,476 patients were identified, of which 3,377 (39.8%) were listed as status-1a and 5,355 (60.2%) had ACLF-3. Patients with ACLF-3 were older and had a greater proportion of males and Hispanics, while those listed as status-1a had the highest proportion of African-Americans. Body mass index was similar among all patient categories. Among patients with ACLF-3, the most common etiology was HCV (34.0%), followed by ALD (23.3%), and then NASH (13.5%). Of the status-1a candidates, 664 (19.7%) were diagnosed with acetaminophen toxicity.

When comparing the severity of liver dysfunction, we observed that patients with ACLF-3 had significantly higher MELD and MELD-Na scores at the time of listing compared with the status-1a patients. Regarding the individual components of the MELD score, individuals listed status-1a had higher INR levels (3.3 vs 2.7, $p<0.001$), while patients with ACLF-3 had greater total serum bilirubin (22.7 vs 8.9, $p<0.001$) and serum creatinine levels (3.7 vs 1.6, $p<0.001$). When evaluating the type and number of specific organ failures among those with ACLF-3, we found liver failure (80.7%) and renal failure (79.8%) to be the most prevalent organ failures in this cohort. The majority of patients were listed with three organ failures (49.8%), while four (32.3%), five (12.4%) and six (4.4%) organ failures at waitlist registration were respectively less prevalent. As the CLIF-SOFA score to determine organ failure has also been validated in ALF(17) we compared the prevalence of organ failures between the two groups. We found that significantly more patients with ACLF-3 had renal (79.8% vs 42.6%, $p<0.001$) and liver failure (80.7% vs 42.4%, $p<0.001$), while more patients listed as status-1a had coagulation failure

(70.9% vs 62.9%, p<0.001), circulatory failure (52.2% vs 46.5%, p<0.001), neurologic failure (57.1% s 52.8%, p<0.001) or needed mechanical ventilation (50.8% vs 42.3%, p<0.001).

Short-term outcomes in the study population

Figure 1 depicts the cumulative incidence of one-year mortality after waitlist registration among the study cohort. Probability of mortality within 14 days after listing was significantly greater for patients with ACLF-3 (27.7%) than those listed as status-1a (19.3%) (p=0.021). In table 2, we subsequently present the outcomes of patients in the two cohorts. Although our primary outcome was 14-day mortality or waitlist removal, we also performed analysis of this outcome 7 and 21 days of listing, to assess the timeframe in which death and transplantation occurred in the two patient groups. When evaluating patient survival within the first 7 days from waitlist registration, we demonstrated that more patients with ACLF-3 survived compared to status-1a patients (47.7% vs 29.6%, p<0.001), whereas the status-1a group had a greater proportion of patients receiving LT (52.4% vs 34.3%, p<0.001). Waiting list mortality or delisting within 7 days was similar between the two groups (17.9% vs 18.0%, p=0.709).

The trend in outcomes shifted, however, such that patient death increased in the ACLF-3 group with 27.7% of patients dying or being removed at 14 days and 32.7% mortality or removal at 21 days after listing (p<0.001). Subsequently, the percentage of patients with ACLF-3 who survived without LT declined over this time period, with 26.1% survival at 14 days and 16.8% at 21 days from waitlist registration (p<0.001). The percentage of patients undergoing LT also increased over 21 days among those with ACLF-3, from 34.3% at 7 days to 46.1% at 14 days and 50.5% at 21 days (p<0.001). In contrast, among the status-1a group, there was also decline in waitlist survival over 21 days and a rise in mortality, but the differences in survival and mortality/removal over time were numerically smaller, and in certain cases not significant. Specifically, the percentage of patients who survived without LT in the status-1a group decreased from 29.6% at 7 days to 24.4% at 21 days from listing (p=0.001), while the proportion

of candidates who died or were removed did not increase significantly, from 17.9% at 7 days to 19.8% at 21 days (p=0.709). These findings suggest that the majority of deaths or waitlist removals among status-1a occur within 7 days of listing, whereas the incidence of mortality continues to increase in the short term for patients with ACLF-3.

In table 3, we provide details regarding waitlist characteristics of the ACLF-3 group, stratified according to 14-day outcomes of survival, transplantation or death. Patients who died or were removed were older (53.4 years) and had greater MELD and MELD-Na scores. Regarding type of organ failure, patients who survived without transplantation had lower prevalence of liver (72.8%), circulatory (50.8%), coagulation (51.8%), and renal (76.0%) failure, as compared to those who died. Patients who were transplanted during this time period had the lowest prevalence of neurologic failure (50.8%), circulatory failure (39.9%), and need for mechanical ventilation (35.3%).

Risk factors associated with 14-day mortality

Table 4, shows the results of four univariable and three multivariable competing risks regression models, utilizing death or waitlist removal within 14 days as the primary outcome and LT as the competing event. In our univariable analysis, we found that patients with ACLF-3 had a significantly greater subhazard ratio for mortality (SHR=1.67, 95% CI: 1.53-1.83) compared to those listed as status-1a. Regarding MELD-Na category, a score of 36-40 did not yield greater short-term mortality compared to a score of < 36, while a score above 40 was significantly associated with mortality within 14 days of listing (SHR=1.49, 95% CI 1.36-1.64). When evaluating MELD-Na score as a continuous variable, our results showed a one-point increase in MELD-Na score led to a 3% increase in likelihood of 14-day mortality.

For our multivariable models, we controlled for additional variables selected *a priori* due to established associations with waitlist mortality including age, gender(18), albumin(19), and etiology of liver disease. In addition, given the improvement in critical care over the last 15 years particularly with regards to fulminant liver failure(20), we also accounted for the time period of

candidate listing, by grouping patients into those listed from 2002-2008 and those listed from 2009-2014. We chose these time periods to provide a similar number of years analyzed between the two eras. Prior to incorporating this variable into the models, we performed descriptive statistics regarding patient outcomes within 14 days of waitlist registration in these two time periods and found lower mortality among patients with ACLF-3 who were listed years 2009-2014. (table S2)

In model 1, we found that when controlling for additional independent variables including MELD-Na category, patients with ACLF-3 had a significantly greater association with waitlist mortality or removal (SHR=1.45, 95% CI 1.31-1.61). Variables that were also associated with mortality or waitlist removal included age (SHR=1.01, 95% CI 1.01-1.02), male gender (SHR=0.90, 95% CI 0.83-0.98), alcoholic liver disease (SHR=0.83, 95% CI 0.75-0.94), and time of listing (SHR=0.89, 95% CI 0.82-0.97). Regarding MELD-Na category, a score of either 36-40 (HR=1.16, 95% CI 1.04-1.29) or greater than 40 (HR=1.51, 95% CI 1.37-1.67) was associated with 14-day mortality.

In model 2, our multivariable analysis incorporated the interaction between ACLF-3 and MELD-Na category and compared it to status-1a listing as the reference. When testing this interaction, our results demonstrated that MELD-Na score < 36 (HR=1.30, 95% CI 1.16-1.47), MELD-Na of 36-40 (HR=1.38, 95% CI 1.22-1.56), and MELD-Na score above 40 (HR=1.77, 95% CI 1.59-1.97) were associated with 14-day mortality or delisting, indicating that when combined with ACLF-3, all three MELD-Na categories portend a higher mortality risk compared to status-1a listing, and this risk increases with greater MELD-Na category. In model 3, we assess MELD-Na score as a continuous variable and find a significant association with ACLF-3 (HR=1.43, 95% CI 1.29-1.59) and MELD-Na score (HR=1.03, 95% CI 1.02-1.03).

Sensitivity analyses

To assess the robustness of our findings, we performed two sensitivity analyses. In the first analysis, we replicated our prior competing risks regression modeling, with incorporation of

MELD score instead of MELD-Na score. Although the MELD-Na score guides current organ allocation policy, previous studies utilized MELD score category as the independent variable when comparing patients listed status-1a with those who have ESLD.(2, 3) Additionally, 1,621 patients had missing MELD-Na scores due to uncollected serum sodium levels from years 2002-2004. As depicted in table S3, ACLF-3 had a consistently greater association with 14-day mortality compared to status-1a listing in all three of the multivariable models.

In the second analysis, we expanded our cohort to include four patient groups: patients listed status-1a, patients without ACLF-3 and MELD score 36-40 (n=1,966), patients without ACLF-3 and MELD score above 40 (n=1,362), and patients with ACLF-3. For this analysis, we categorized the non-ACLF-3 groups according to MELD score instead of MELD-Na score, since the MELD-Na score was missing in 1,621 patients. The baseline characteristics and 14-day outcomes from time of listing for patients without ACLF-3 are described in table S4. The results from both univariable and multivariable regression demonstrated ACLF-3 to have the strongest association with mortality or removal at 14 days from listing (SHR=1.75, 95% CI 1.59-1.93). Consistent with findings from previous studies, among patients without ACLF-3, a MELD score of 36-40 did not confer additional risk of mortality compared to status-1a listing (SHR=1.09, 95% CI 0.97-1.24), while a score above 40 was associated with greater risk of death within 14 days (SHR=1.68, 95% CI 1.47-1.98).(2, 3)

Post-transplant survival probability

In figure 2a and table S6, we report survival probability through one-year post-transplantation in the two groups. At one-year from transplantation, patients listed as status-1a had an 82.5% survival probability, whereas those with ACLF-3 had a survival probability of 79.8%. As the proportional hazards assumption was not met, we could not perform statistical testing to assess differences in the survivor function.

Discussion

Our study, which is the first to compare short-term waitlist mortality between patients listed status-1a and candidates with ACLF-3, reveals several important findings. First, we characterize trends in clinical outcomes after listing and demonstrate a rising prevalence in mortality without transplantation over 21 days among ACLF-3 patients, versus a stagnant trend in mortality among status-1a patients during this same period. Secondly, we show that ACLF-3 confers a consistently higher risk of waitlist mortality or delisting within 14 days compared to status-1a listing, independent of MELD or MELD-Na score. Thirdly, we demonstrate that the interaction between ACLF-3 and MELD or MELD-Na category is associated with waitlist mortality, even in patients with a score < 36. Finally, we establish that early transplantation for ACLF-3 markedly improves prognosis, and the one-year survival probability after LT for the status-1a and ACLF-3 groups are numerically similar, specifically within 3 percentage points of each other.

In the current organ allocation system, patients listed status-1a benefit from both greater priority for transplantation and broader organ sharing, due not only to their high risk of mortality without LT but also the rapidity in which hepatic deterioration occurs.(21) Furthermore, current guidelines(22) emphasize the importance of early recognition of this condition, in order to expedite transplant evaluation and listing. Therefore, status-1a candidates with ALF have the highest chance of receiving LT, even though transplant-free survival in this population has improved from 32.9% to 61.0%, since 1998.(20) Patients with ACLF-3, however, face a number of challenges that disadvantage them in the current system, despite our findings that they are at greater risk of short-term mortality. First, transplant priority for these patients is guided by the MELD-Na score, which does not account for extra-hepatic organ failures and therefore may not fully reflect prognosis.(11) Secondly, candidates listed status-1a may remain high on the waitlist, even though stabilization of their condition may actually lead to full recovery of liver function.

Patients with ACLF-3, however, will continue to be at high risk of death from intra and extra-hepatic organ failure, even after their condition has initially stabilized and their MELD-Na score has decreased. Therefore, as shown in our study, waitlist mortality without transplantation rises in this population over time, though it tends to be stable among patients listed status-1a.

It is further notable that the subhazard ratio for mortality associated with ACLF-3 remains significant even when controlling for the MELD or MELD-Na score. This finding was not demonstrated in prior studies comparing status-1a listing to high MELD score in patients with ESLD alone.(2, 3) There may be several reasons for this finding. On a clinical level, the MELD score does not account for ACLF due to extra-hepatic organ failures, which appears to be a distinct entity from ACLF secondary to hepatic failure with greater associated mortality.(9) Furthermore, on a pathophysiological level, evidence suggests that ACLF is a distinct disease entity from decompensated cirrhosis, for which the MELD score was originally derived and validated. Beyond the differences regarding greater systemic inflammation, oxidative stress, and circulatory dysfunction,(4, 6-8) more recent evidence suggests that the INR, which is the most heavily weighted component of the MELD score, may not fully gauge coagulopathy or liver dysfunction in ACLF.(23) In a study by Blasi et al, patients with ACLF were found to have a greater prevalence of several domains of hypocoagulability not measured by the INR including, time to fibrin formation and clot firmness.(23) These differences in coagulation between ACLF and decompensated cirrhosis reflected not only bleeding risk but also greater systemic inflammation and short-term mortality.

In the study by Sharma et al, the authors proposed assigning similar transplant priority for patients listed status-1a to those with ESLD and a MELD score above 40.(2) Although we believe further validation of our findings is needed before recommending this, we do have other suggestions to improve the care of patients with ACLF-3. First, we emphasize the early recognition of ACLF-3, and once identified, such patients should undergo rapid transplant evaluation, similar to what is suggested for individuals with ALF.(22) Unfortunately,

implementing this suggestion is difficult due to the lack of a unified definition for ACLF(24) to enable clinicians to identify this condition. Therefore, we believe it is imperative that formal consensus criteria are developed around identifying ACLF, to allow for transplant centers to create policy regarding evaluation and listing of these patients, particularly those with more than one organ failure. Secondly, our results demonstrate that the strongest association with short-term waiting list mortality occurred with the interaction MELD-Na score above 40 and ACLF-3, but this interaction also yielded greater risk of 14-day mortality than that of status-1a candidates across all MELD-Na categories. This finding provides further evidence that the MELD-Na score does not predict short-term mortality equally between patients with decompensated cirrhosis and ACLF-3, and determining waiting list priority for ACLF-3 patients may require a scoring system that incorporates organ failures not captured by the MELD-Na score.

Ultimately, the goal of these recommendations is to facilitate LT for ACLF-3. Our results show that mortality after LT is numerically similar at one year between patients listed status-1a and with ACLF-3. This finding is consistent with those of prior studies, which have demonstrated that most deaths after LT for ALF occur within three months due to infection or neurologic complications.(25, 26) In the ACLF-3 population, the absence of mechanical ventilation at the time of LT may further improve 1-year survival probability to approximately 85%.(11) As transplantation markedly improves the survival among candidates with ACLF-3, additional strategies should be considered in caring for this population including LT after stabilization of organ failures(27) or judicious use of living donor organ transplant.(28)

The UNOS registry has certain advantages for this investigation, particularly the availability of a large sample size of patients listed as status-1a and with ACLF-3, across multiple regions in the United States. However, several limitations exist regarding our analysis, which we will discuss in detail. First, there is the potential for misclassification at listing. For instance, it is possible that certain individuals were incorrectly classified as not having ACLF-3 though they 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, 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. Thirdly, ACLF is a heterogeneous condition and our study only evaluates patients with ACLF who are listed for transplantation in the United States, with exclusion of those receiving exception points. Therefore, we cannot account for the outcomes of patients who were declined for transplantation listing, not referred to a transplant center, or listed with a MELD exception. Subsequently, our study is designed specifically to address questions related to LT in this population and we recommend caution in extrapolating our findings to describe the natural history ACLF-3. Finally, organ allocation for LT is evolving and new rules may soon be implemented to distribute organs based partially on distance from the donor hospital. Therefore, it is possible that under this new policy, 14-day waiting list mortality for ACLF-3 would be reduced as more patients with this condition are transplanted. This is a limitation our study cannot address. However, we believe our results are nonetheless important since under the newly created distribution policy, priority for ACLF-3 candidates will remain guided by the MELD-Na score, and the greatest urgency and broadest geographic sharing will still be provided to patients listed as status-1a. Therefore, data regarding the high short-term waitlist mortality of ACLF-3 patients relative to status-1a candidates and the limitations in the MELD-Na scoring system in predicting these outcomes is valuable in guiding future research regarding optimization of organ distribution.

In conclusion, ACLF-3 is associated with greater risk of 14-day waitlist mortality compared to those listed status-1a, and this association occurs independently of the MELD-Na score. Additionally, transplantation for selected patients with ACLF-3 dramatically increases

survival, and post-transplant mortality at 1-year for these patients is numerically similar to that of recipients listed status-1a. These findings illustrate the importance of early recognition and rapid transplant evaluation for these patients, along with consideration for additional priority for organ allocation, to enable LT within a shorter time frame.

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Figure 1. Cumulative incidence of waitlist mortality within 14 days of registration (p=0.021)

Figure 2. One-year post-transplant survival among patients transplanted within 14 days of waitlist registration

Table 1. Baseline characteristics of the study population at waitlist registration

Characteristics	**Status 1a (n=3,377)**	**ACLF-3 (n=5,099)**	**p-value**
Age, mean (SD)	42.9 (14.5)	51.8 (10.6)	<0.001
Male, n (%)	1,273 (37.8)	3,149 (61.6)	<0.001
Race, n (%)			<0.001
Caucasian	2,154 (63.7)	3,289 (64.5)	0.499
African-American	547 (16.2)	646 (12.7)	
Hispanic	375 (11.1)	827 (16.2)	
Acetaminophen toxicity	664 (19.8)		
Etiology of cirrhosis, n (%)			
NASH		690 (13.5)	
HCV		1,734 (34.0)	
ALD		1,189 (23.3)	
Other		1,486 (29.1)	
Body mass index, median (IQR)	26.9 (23.3-31.5)	28.5 (24.7-33.2)	0.002
Diabetes mellitus, n (%)	346 (10.6)	1,113 (22.6)	<0.001
Albumin, median (IQR)	2.8 (2.4-3.2)	3 (2.5-3.5)	0.001
Portal vein thrombosis, n(%)	133 (4.2)	282 (5.9)	0.001
MELD score, median (IQR)	34.5 (28.8-40.8)	39.3 (34.4-43.6)	
MELD-Na score, median (IQR)	34.7 (28.9-40.9)	39.2 (34.9-42.9)	<0.001
Total bilirubin, median (IQR)	8.9 (4.2-20.9)	22.7 (13.7-33.3)	<0.001
Creatinine, median (IQR)	1.6 (1-3.4)	3.7 (2.1-4)	<0.001
INR, median (IQR)	3.3 (2.3-5.1)	2.7 (2.0-3.3)	<0.001
Organ failure			
Liver failure, n (%)	1,429 (42.4)	4,110 (80.7)	<0.001
Mechanical ventilation, n (%)	1,715 (50.8)	2,157 (42.3)	<0.001
Circulatory failure, n (%)	1,757 (52.2)	2,372 (46.5)	<0.001
Coagulation failure, n (%)	2,396 (70.9)	3,212 (62.9)	<0.001
Neurologic failure, n (%)	1,928 (57.1)	2,694 (52.8)	<0.001
Renal failure, n (%)	1,438 (42.6)	4,078 (79.8)	<0.001
Hemodialysis, n (%)	498 (14.8)	1,906 (37.6)	<0.001
Number of organ failures:			
Four	1,393 (41.3)	1,648 (32.3)	<0.001
Five	637 (18.9)	685 (12.4)	0.002
Six	137 (4.1)	225 (4.4)	0.424

Table 2. Outcomes of the patient cohort within 7, 14 and 21 days of waitlist registration

	Status 1a				ACLF-3			
Total population	**7 days**	**14 days**	**21 days**	**p-value***	**7 days**	**14 days**	**21 days**	**p-value***
Survived without transplantation, n (%)	1,001 (29.6)	855 (25.3)	825 (24.4)	0.001	2,432 (47.7)	1,334 (26.1)	858 (16.8)	<0.001
Transplanted, n (%)	1,771 (52.4)	1,870 (55.3)	1,882 (55.7)	0.001	1,748 (34.3)	2,349 (46.1)	2,573 (50.5)	<0.001
Died/removed, n (%)	605 (17.9)	652 (19.3)	670 (19.8)	0.709	919 (18.0)	1,416 (27.7)	1,668 (32.7)	<0.001

*P-values represent significance of trend, evaluated by Wilcoxon type trend test

Table 3. Comparison of patient characteristics of ACLF-3 patients, grouped according to survival, transplantation, or mortality within 14 days of listing

	Survived without transplantation (n=1,334)	**Transplanted (n=2,349)**	**Died or removed (n=1,416)**	**p-value**
Age, mean (SD)	50.8 (11.1)	51.2 (10.5)	53.4 (10.2)	<0.001
Male, n (%)	813 (60.9)	1,484 (63.2)	852 (60.2)	0.143
Race, n (%)				0.225*
Caucasian	882 (66.1	1,488 (63.4)	919 (64.9)	
African American	157 (11.8)	315 (13.4)	174 (12.3)	
Hispanic	216 (16.2)	390 (16.6)	221 (15.6)	
MELD score, median (IQR)	36.5 (30.7-41.8)	39.6 (35.2-43.4)	41.0 (36.2-44.9)	<0.001
MELD-Na score, median (IQR)	36.9 (31.8-41.5)	40 (35.8-42.7)	40.8 (36.6-44)	0.001
Diabetes, n (%)	290 (22.5)	503 (22.0)	320 (23.8)	0.471
Body mass index (median, IQR)	27.9 (24.3-32.9)	28.6 (24.9-33.1)	28.7 (24.9-33.5)	0.574
Portal vein thrombosis, n (%)	77 (6.2)	141 (6.3)	64 (4.9)	0.208
Etiology, n (%)				
NASH	181 (13.7)	304 (12.8)	205 (14.5)	0.410
HCV	405 (30.4)	824 (35.1)	505 (35.7)	0.004
ALD	323 (24.0)	581 (24.7)	285 (20.1)	0.004
Liver failure, n (%)	970 (72.8)	1,968 (83.9)	1,172 (82.8)	<0.001
Mechanical ventilation, n (%)	620 (46.5)	829 (35.3)	708 (50.0)	<0.001
Circulatory failure, n (%)	677 (50.8)	937 (39.9)	758 (53.5)	<0.001
Coagulation failure, n (%)	691 (51.8)	1,574 (67.0)	947 (66.9)	<0.001
Neurologic failure, n (%)	728 (54.6)	1,194 (50.8)	772 (54.5)	0.030
Renal failure, n (%)	1,014 (76.0)	1,891 (80.5)	1,173 (82.8)	<0.001
Organ failures:				
Four	396 (27.7)	653 (27.8)	599 (42.3)	<0.001
Five	140 (10.5)	274 (11.6)	271 (19.1)	<0.001
Six	32 (2.3)	81 (3.5)	113 (7.9)	<0.001

Table 4. Univariable and multivariable Fine and Gray competing risks regression regarding mortality within 14 days from waitlist registration

	Univariable model SHR (95% CI)	**Multivariable model 1 SHR (95% CI)**	**Multivariable model 2* SHR (95% CI)**	**Multivariable model 3** SHR (95% CI)**
Status 1a	Reference	Reference	Reference	Reference
ACLF-3	1.67 (1.53-1.83)	1.45 (1.31-1.61)		1.43 (1.29-1.59)
MELD-Na score < 36	Reference	Reference	1.30 (1.16-1.47)*	
MELD-Na score 36-40	1.06 (0.96-1.17)	1.16 (1.04-1.29)	1.38 (1.22-1.56)*	
MELD-Na score > 40	1.49 (1.36-1.64)	1.51 (1.37-1.67)	1.77 (1.59-1.97)*	
MELD-Na score	1.03 (1.02-1.03)			1.03** (1.02-1.03)
Age		1.01 (1.01-1.02)	1.01 (1.01-1.01)	1.01 (1.01-1.02)
Male		0.90 (0.83-0.98)	0.91 (0.83-0.98)	0.90 (0.83-0.98)
Albumin		1.00 (0.95-1.06)	1.04 (0.98-1.08)	1.01 (0.96-1.07)
HCV		0.93 (0.84-1.03)	0.94 (0.86-1.03)	0.93 (0.84-1.03)
ALD		0.83 (0.75-0.94)	0.85 (0.76-0.95)	0.84 (0.75-0.94)
Listed, years 2009-2014		0.89 (0.82-0.97)	0.87 (0.81-0.95)	0.89 (0.82-0.97)

*Interaction between ACLF-3 and MELD-Na category
**MELD-Na analyzed as continuous variable

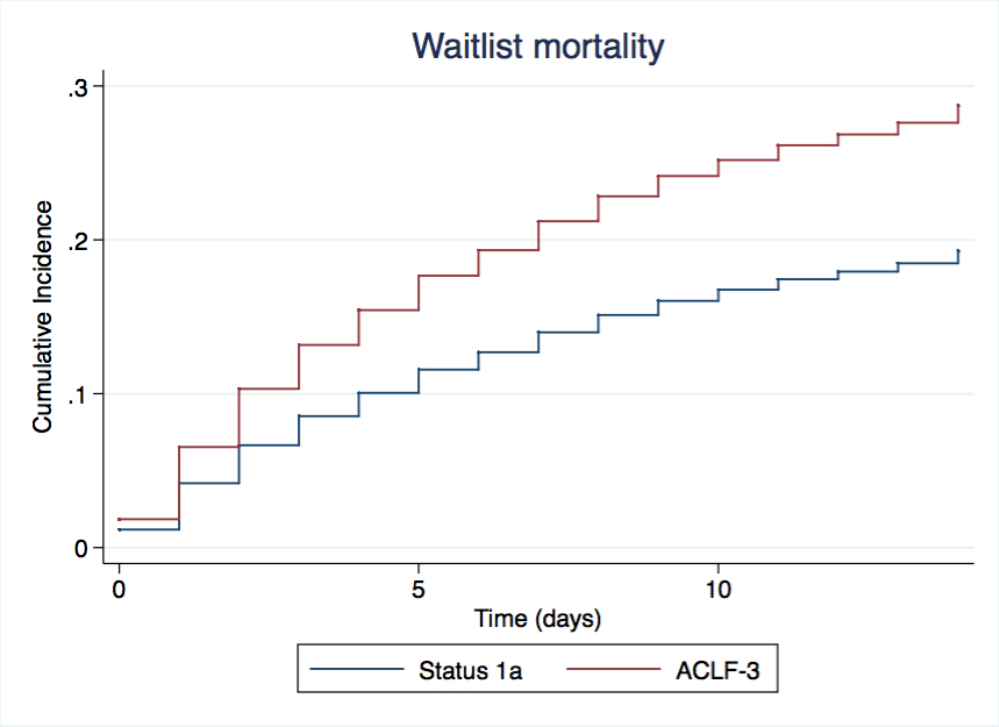

Figure 1. Cumulative incidence of waitlist mortality within 14 days of registration (p=0.021)

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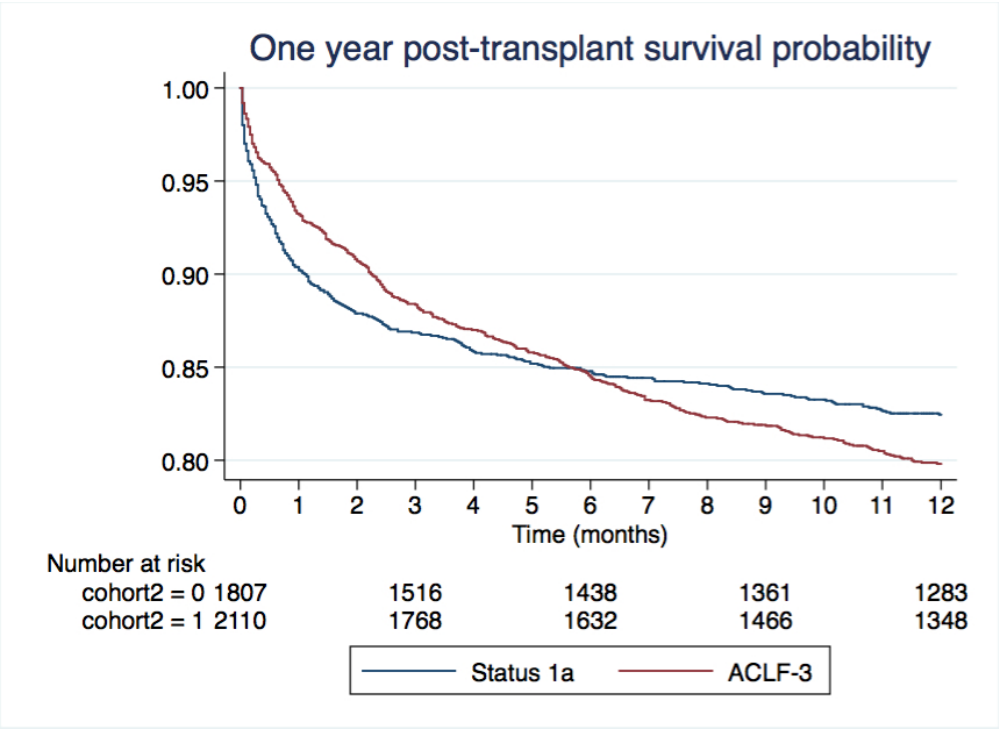

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Table S1. Criteria to determine presence of organ dysfunction/failure

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. Comparison of outcomes within 14 days of waitlist registration, among patients listed as status 1a or with ACLF-3, according to time period of listing

	Status 1a			ACLF-3		
Total population	**2002-2008**	**2009-2014**	**p-value**	**2002-2008**	**2009-2014**	**p-value**
Survived without transplant, n (%)	377 (26.1)	478 (24.7)	0.341	556 (26.5)	725 (25.8)	0.575
Transplanted, n (%)	786 (54.5)	1,084 (56.0)	0.382	924 (44.1)	1,350 (48.0)	0.006
Died, n (%)	279 (19.4)	919 (19.3)	0.899	618 (29.5)	736 (26.2)	0.011
Days before LT, Median (IQR)	2 (1-3)	2 (1-3)	0.162	4 (2-8)	4 (2-8)	0.508
Days before mortality, Median (IQR)	2 (1-3)	2 (1-4)	0.593	5 (3-9)	6 (3-9)	0.242

Table S3. Univariable and multivariable Fine and Gray competing risks regression regarding mortality within 14 days from waitlist registration, utilizing MELD score

	Univariable model HR (95% CI)	**Multivariable model 1 HR (95% CI)**	**Multivariable model 2* HR (95% CI)**	**Multivariable model 3** HR (95% CI)**
Status 1a	Reference	Reference	Reference	Reference
ACLF-3	1.67 (1.53-1.83)	1.50 (1.36-1.67)		1.48 (1.34-1.64)
MELD score < 36	Reference	Reference	1.30 (1.16-1.47)*	
MELD score 36-40	1.07 (0.98-1.17)	1.22 (1.10-1.36)	1.38 (1.22-1.56)*	
MELD score > 40	1.48 (1.37-1.61)	1.53 (1.40-1.67)	1.77 (1.59-1.97)*	
MELD score**	1.03 (1.02-1.03)			1.03 (1.02-1.03)*
Age		1.01 (1.01-1.02)	1.01 (1.01-1.01)	1.01 (1.01-1.02)
Male		0.88 (0.81-0.95)	0.91 (0.83-0.98)	0.88 (0.81-0.95)
Albumin		1.00 (0.95-1.06)	1.04 (0.98-1.08)	1.00 (0.95-1.06)
HCV		0.95 (0.87-1.04)	0.94 (0.86-1.03)	0.95 (0.87-1.04)
ALD		0.84 (0.76-0.94)	0.85 (0.76-0.95)	0.84 (0.76-0.94)
Listed, years 2009-2014		0.86 (0.79-0.93)	0.87 (0.81-0.95)	0.86 (0.79-0.93)

*Interaction between ACLF-3 and MELD category
**MELD analyzed as continuous variable

Table S4. Baseline characteristics and outcomes within 14 days of waitlist registration, among patients end-stage liver disease without ACLF-3, according to MELD category

Characteristics	**MELD 36-40 (n=1,966)**	**MELD > 40 (n=1,362)**
Age, mean (SD)	50.6 (11.8)	47.6 (12.8)
Male, n (%)	1,230 (62.6)	817 (59.9)
Race, n (%)		
Caucasian	1,262 (64.2)	853 (62.5)
African American	285 (14.5)	225 (16.5)
Hispanic	298 (15.2)	192 (14.1)
Etiology, n (%)		
NASH	292 (14.9)	161 (11.8)
HCV	549 (27.9)	327 (24.1)
ALD	454 (23.1)	237 (17.4)
MELD score, median (IQR)	37.7 (36.8-38.6)	41.2 (42.6-45.2)
Total bilirubin, median (IQR)	19.5 (9.5-31.1)	25 (9.8-36.4)
Creatinine, median (IQR)	3.7 (2.0-4.0)	4 (2.9-4.7)
INR, median (IQR)	2.3 (1.9-3.4)	3 (2.1-5.7)
BMI, median (IQR)	28.3 (4.4-33.1)	27.5 (24.0-32.9)
Diabetes mellitus, n (%)	438 (23.1)	236 (28.4)
Albumin, median (IQR)	2.9 (2.4-3.4)	2.9 (2.4-3.4)
Portal vein thrombosis, n(%)	88 (4.8)	51 (4.2)
Outcomes		
Survived, n (%)	628 (31.9)	332 (24.4)
Transplanted, n (%)	1,050 (53.4)	630 (53.6)
Died, n (%)	288 (14.7)	300 (22.0)

Table S5. Univariable and multivariable Fine and Gray competing risks regression regarding mortality within 14 days from waitlist registration, with inclusion of patients without ACLF-3

	Univariable model HR (95% CI)	**Multivariable HR (95% CI)**
Status 1a	Reference	Reference
No ALCF-3, MELD score 36-40	0.98 (0.87-1.09)	1.09 (0.97-1.24)
No ACLF-3, MELD score > 40	1.27 (1.12-1.43)	1.68 (1.47-1.91)
ACLF-3	1.69 (1.55-1.84)	1.75 (1.59-1.93)
Age		1.01 (1.01-1.02)
Male		0.92 (0.86-0.98)
Albumin		0.89 (0.86-0.93)
HCV		0.95 (0.88-1.03)
ALD		0.80 (0.72-0.86)
Listed, years 2009-2014		0.86 (0.79-0.93)

Table S6. One year post-transplant survival probability among patients transplanted within 14 days of waitlist registration

	Patient survivor function (95% CI)			
	1 month	**3 months**	**6 months**	**12 months**
Status 1a	0.902 (0.888-0.915)	0.868 (0.852-0.883)	0.845 (0.830-0.864)	0.825 (0.806-0.842)
ACLF-3	0.932 (0.920-0.942)	0.884 (0.868-0.896)	0.845 (0.823-0.859)	0.798 (0.779-0.815)