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Patients with severe acute-on-chronic liver failure are disadvantaged by model for end-stage liver disease based organ allocation policy

Short Title: Waitlist outcomes for ACLF in patients with high MELD-Na scores

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List of Abbreviations:
Acute-on-chronic liver failure (ACLF)
Confidence interval (CI)
International normalized ratio (INR)
Model for end-stage liver disease-sodium (MELD-Na)
Sub-hazard ratio (SHR)
United Network for Organ Sharing (UNOS)

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Abstract

Background: Mortality for patients with acute-on-chronic liver failure (ACLF) may be underestimated by the model for end-stage liver disease-sodium (MELD-Na) score.

Aim: Our aim was to assess waitlist outcomes across varying grades of ACLF among a cohort of patients listed with a MELD-Na score ≥ 35, and therefore having similar priority for liver transplantation.

Methods: We analyzed the United Network for Organ Sharing (UNOS) database, years 2010-2017. Waitlist outcomes were evaluated using Fine and Gray's competing risks regression.

Results: We identified 6,342 candidates at listing with a MELD-Na score>=35, of which 3,122 patients had ACLF-3. Extra-hepatic organ failures were present primarily in patients with 4-6 organ failures. Competing risks regression revealed that candidates listed with ACLF-3 had a significantly higher risk for 90-day waitlist mortality (Sub-hazard ratio (SHR)=1.41; 95% confidence interval (CI) 1.12-1.78) relative to patients with lower ACLF grades. Subgroup analysis of ACLF-3 revealed that both the presence of 3 organ failures (SHR=1.40, 95% CI 1.20-1.63) or 4-6 organ failures at listing (SHR=3.01; 95% CI 2.54-3.58) was associated with increased waitlist death. Candidates with 4-6 organ failures also had the lowest likelihood of receiving liver transplantation (SHR=0.61, 95% CI 0.54-0.68). The Share 35 rule was associated with reduced 90-day waitlist mortality among all patients listed with ACLF-3 and MELD-Na score >35 (SHR=0.59; 95% CI 0.49-0.70). However, Share 35 rule implementation was not associated with reduced waitlist mortality among patients with 4-6 organ failures (SHR=0.76; 95% CI 0.58-1.02).

Conclusion: The MELD-Na score disadvantages patients with ACLF-3, both with and without extra-hepatic organ failures. Incorporation of organ failures into allocation policy warrants further exploration.

Keywords: UNOS database; organ failure; liver transplantation

Introduction

Acute-on-chronic liver failure (ACLF) is associated with severe systemic inflammation and high 28-day mortality.(1-3) The short-term mortality of patients with ACLF grade 3 (ACLF-3), defined as the development of three or more organ failures,(1) is particularly high, approaching 80% at 28-days (4-6) and possibly surpassing that of acute liver failure.(7) Given the high mortality associated with ACLF-3 and lack of indicated pharmacologic treatment, liver transplantation may be the only viable option in certain patients with this syndrome. Though the model for end-stage liver disease-sodium (MELD-Na) score has improved equity regarding organ allocation, recent findings have suggested that it may not fully capture waitlist mortality among certain patients with ACLF-3, as candidates with ACLF-3 and a MELD-Na score < 25 have the highest percentage of death or waitlist removal within 28 days of listing.(8)

However, as the majority of patients with ACLF-3 listed in the United States have a MELD-Na score ≥ 35(8), it can be argued that these individuals are adequately prioritized for liver transplantation, especially since the implementation of regional sharing.(9, 10) However, while the MELD-Na score is well validated to determine prognosis for patients with decompensated cirrhosis, ACLF is distinct from decompensated cirrhosis, regarding inflammatory cytokine release, response to medical therapy, and short-term mortality.(1, 11, 12) Furthermore, the development of respiratory, circulatory, or brain failure, is not accounted for in the MELD-Na score but is associated with a higher risk of mortality relative to intrahepatic organ failures(2) and occurs most commonly in individuals with ACLF-3.(1) Additional research is therefore necessary to determine whether discrepancies exist regarding waitlist mortality across different grades of ACLF, particularly among a group of candidates with similarly high MELD-Na scores, and who should therefore be

prioritized for liver transplantation equally. Accordingly, our primary aim was to evaluate the differences in short-term waitlist outcomes according to the grade of ACLF among a cohort of listed patients with a MELD-Na score ≥ 35, focusing on the impact of intra and extra-hepatic organ failures.

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.(13)

Study population

Utilizing the UNOS registry, we evaluated patients age 18 years or older listed for liver transplantation from 2010 to 2017. We excluded patients listed status-1a, who received MELD exception points, who were re-transplanted, and who underwent multiple organ transplantation, aside from simultaneous liver and kidney transplant. In the final cohort, there were no patients who underwent living donor liver transplantation. We collected data encompassing characteristics at the time of waitlist registration, as well as information regarding waitlist outcomes and post-liver transplantation outcomes. MELD-Na score at listing was rounded to the nearest whole number and capped at a score of 40. Serum creatinine was capped at 4 mg/dL. Regarding the etiology of liver disease, patients were considered as having nonalcoholic steatohepatitis as their primary cause of cirrhosis if they were identified either as having nonalcoholic steatohepatitis related cirrhosis or cryptogenic cirrhosis with a concurrent diagnosis of diabetes mellitus or a body mass index above 30 kg/m2, as done in previous studies.(14, 15) To create the final analytic cohort, we included patients with a MELD-Na ≥35 at waitlist registration, and excluded patients listed for retransplantation, multiple organ transplantation, as status-1a, or with MELD exception points.

Identification of ACLF

ACLF at the time of waitlist registration was identified based on the European Association for the Study of the Liver-Chronic Liver Failure criteria of having a hepatic decompensation of either ascites or hepatic encephalopathy and the presence 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.(1) (Table S1) Although bacterial infection and variceal hemorrhage are also decompensating events, information regarding these conditions was unavailable in the UNOS database. Specific organ failures were determined according to the CLIF consortium organ failures score for coagulopathy, liver failure, renal dysfunction and renal failure, neurologic failure, and circulatory failure.(1) We used mechanical ventilation as a surrogate marker for respiratory failure. Grade of ACLF was determined based on the number of organ failures at listing and at transplantation. (Table S1)

Statistical analysis

All statistical analyses were performed using the Stata statistical package (version 14, Stata Corporations, Texas). Comparisons were made utilizing Chi-square testing for categorical variables and analysis of variance or Wilcoxon rank-sum testing for continuous variables between groups. We assessed for risk factors related to waitlist mortality using Fine and Gray's competing risks regression, where liver transplantation was the competing event, along with creation of cumulative incidence functions. For the outcome of waitlist mortality, we combined death and removal due to being too sick into a single outcome. Variables for our models were selected *a priori.* To account for waitlist time, we created a variable for region of transplantation, according to median meld score at time of transplant as follows: low (regions 3, 6, 10, and 11), medium (regions 2, 4, and 8), and high (regions

1, 5, 7, and 9) MELD regions. As there was less than 5% missing data for each variable in our model, we did not perform imputation for missing data. Post-transplant survival was assessed with Kaplan-Meier methods, with differences evaluated using log-rank testing. Tests of the proportional hazards assumption were assessed using scaled Schoenfeld residuals. Goodness of fit was tested using Cox-Snell residuals.

Results

Baseline characteristics and short-term outcomes

A total of 6,342 patients listed with a MELD-Na score ≥ 35 at the time of listing were studied (Figure S1), of which 3,122 (49.2%) had ACLF-3, 2,523 (39.8%) had ACLF-2, 560 (8.8%) had ACLF-1, and 137 (2.2%) had no ACLF. Table 1 illustrates the baseline characteristics of the study population at waitlist registration, as well as outcomes within 90 days of listing. Patients with ACLF-1 were older (54.7 years, p<0.001). There were no differences regarding gender or ethnicity among the four patient groups. Alcoholic liver disease was the predominant etiology of cirrhosis among all patient groups. With regards to the prevalence of specific organ system failures, certain patients with no ACLF developed liver failure (65.7%), coagulation failure (55.5%) and circulatory failure (6.6%). Notably, 28.4% of patients were identified as having renal failure, but were categorized as having no ACLF since they were not categorized as having ascites or hepatic encephalopathy at listing. Among candidates with ACLF-3, the most prevalent organ failures were renal (92.5%), liver (88.1%), and coagulation failure (72.0%). Additionally, the majority of patients listed with ACLF-3 had 3 organ system failures (70.9%), while 29.1% were listed with 4-6 organ system failures.

Waitlist outcomes

Individuals with ACLF-3 at listing had the highest mortality (p<0.001) at 28 days (30.4%) and 90 days (32.5%) and the shortest median time between listing (7 days, p<0.001) (Table 1). Candidates with ACLF-2 comprised largest percentage of patients transplanted within 90 days of listing (74.7%, p<0.001). In table 2, we display univariable and multivariable competing risks regression analysis of factors associated with mortality or liver transplantation within 90 days of waitlist registration. Due to the small number of

patients in the cohort with no ACLF or ACLF-1, we combined these patients to create the reference group. Cumulative incidence functions concerning death on the waiting list or liver transplantation are displayed in figures S2 and S3. Relative to patients without ACLF, candidates with ACLF-3 had a significantly greater risk of 90-day mortality relative to patients without ACLF or with ACLF-1 (Sub-hazard ratio (SHR)=1.41, 95% confidence interval (CI) 1.12-1.78), though this was not the case among those with ACLF-2 (SHR=0.96, 95% CI 0.76-1.16). Candidates with ACLF-2 at listing had the highest likelihood of transplantation within 90 days (SHR=1.17, 95% CI 1.04-1.31).

Sensitivity analyses

As the risk of mortality in our cohort may be concentrated within the first 14 days after waitlist registration, particularly for candidates listed with ACLF-3, we performed a sensitivity analysis regarding death within 7 and 14 days after listing. Our competing risks model was adjusted for age, MELD-Na score, gender, race, etiology of liver disease and region. Relative to patients without ACLF or with ACLF-1, we found both ACLF-2 (SHR=1.87, 95% CI 1.46-2.39) and ACLF-3 (SHR=4.72, 95% CI 3.67-6.06) to have a significantly greater risk of mortality within 7 days of listing. Similar findings were demonstrated when analyzing mortality within 14 days of listing, for both ACLF-2 (SHR=1.58, 95% CI 1.32-1.89) and ACLF-3 (SHR=3.61, 95% CI 2.98-4.36).

Additionally, as we could not definitively determine which patients had renal failure at waitlist registration due to chronic kidney disease, we performed another sensitivity analysis by repeating our multivariable competing risks model for 90-day waitlist mortality, after removal of 1,256 patients who underwent simultaneous liver and kidney transplantation. We demonstrated that candidates with ACLF-3 had a higher likelihood for

mortality (SHR=1.41, 95% CI 1.08-1.82), compared to patients without ACLF or with ACLF-1, while those with ACLF-2 did not (SHR=0.94, 95% CI 0.75-1.14).

Organ failures

We compared characteristics at waitlist registration among patients listed with ACLF-3 who died (n=1,105) or were transplanted (n=2,016) within 90 days, focusing on the number and type of organ system failures. (Table S2) Those who died were older (53.8 years, p<0.001), though there was no difference in gender or MELD-Na score between the two groups. Concerning specific organ failures, the prevalence of liver failure, renal failure and coagulation failure were similar between the two groups, but patients who died had a significantly greater percentage of circulatory failure (48.3% vs 33.6%, p<0.001), need for mechanical ventilation (40.9% vs 23.9%, p<0.001) and brain failure (51.4% vs 47.6%, p=0.048). Additionally, there was a greater proportion of patients with 4-6 organ failures among those who died, compared to patients who were transplanted (40.5% vs 23.7%, p<0.001). Multivariable competing risks regression (Table 3), adjusted for age and MELD-Na score, further corroborated these findings by demonstrating mechanical ventilation (SHR=1.98, 95% CI 1.75-2.24), circulatory failure (SHR=1.71, 95% CI 1.52-1.94) and brain failure (SHR=1.16, 95% CI 1.03-1.33) to be significantly associated with waitlist mortality within 90 days of waitlist registration among patients with ACLF-3.

Subgroup analysis of ACLF-3

As prior studies have demonstrated that the development of 4-6 organ system failures yields the highest mortality among patients with ACLF(16), we assessed waitlist outcomes after subdividing candidates with ACLF-3 into those with 3 organ failures and those with 4-6 organ failures. Table S3 summarizes baseline characteristics and 90-day

outcomes among patients with ACLF-3 who had 3 organ failures (n=2,213) or 4-6 organ failures (n=909). The group with 4 or more organ failures had a greater percentage of patients requiring mechanical ventilation (96.9% vs 2.1%, p<0.001), circulatory failure (100.0% vs 13.3%, p<0.001) and brain failure (61.4% vs 43.7%, p<0.001), whereas patients with 3 organ failures had a greater percentage of liver failure (89.4% vs 84.8%, p<0.001) and coagulation failure (79.5% vs 53.7%, p<0.001). The prevalence of renal failure was similar between the two groups. Among the 2,213 patients with 3 organ failures alone, 1,407 (63.5%) had a combination of liver failure, renal failure and coagulation failure, of whom 386 (27.4%) died within 28 days of listing.

In table 4, we display univariable and multivariable competing risks regression analysis, regarding death or transplantation within 28-days of listing. In this analysis, we compared three groups: candidates listed with no ACLF or ACLF grades 1 or 2 (ACLF 0-2), candidates listed with ACLF-3 and three organ failures, and candidates listed with ACLF-3 and 4-6 organ failures. A time point of 28 days instead of 90 days was chosen, given previous data indicating 90% mortality by 28 days among patients who developed ACLF with 4-6 organ failures.(16) Multivariable analysis demonstrated that relative to ACLF 0-2, patients with 3 organ failures (SHR=1.40, 95% CI 1.20-1.63) had greater association with mortality. However, this association was even more pronounced among patients with 4-6 organ failures (SHR=3.01, 95% CI 2.54-3.58). In an evaluation of factors related to liver transplantation, we found that patients with 3 organ failures had a similar likelihood of undergoing transplantation within 28 days (SHR=1.01, 95% CI 0.94-1.09) compared to patients without ACLF or ACLF grade 1-2, while those with 4-6 organ failures had a significantly lower likelihood of receiving liver transplantation (SHR=0.61, 95% CI 0.54-0.68). (Figures 1a and 1b) Similar findings were demonstrated after removal of

patients who underwent simultaneous liver and kidney, regarding candidates with 3 organ failures (SHR=1.36, 95% CI 1.15-1.61) and 4-6 organ failures (SHR=3.12, 95% CI 2.58-3.78).

Impact of Share 35

We performed additional analysis regarding whether the probability of mortality or liver transplantation was impacted after implementation of regional sharing. This aspect of the study was restricted to patients with ACLF-3, since this subgroup of patients had the greatest likelihood of waitlist death. As the Share 35 rule was enacted in June 2013, we created a variable for the pre and post-Share 35 era, where the pre-Share 35 time period included patients listed from years 2010-2012 and the post-Share 35 time period evaluated patients who were listed from years 2014-2016. A total of 2,315 candidates were studied in this analysis, of which 994 (42.9%) were listed in the pre-Share 35 era and 1,321 (57.1%) were listed after implementation of the Share 35 rule. Table S4 describes baseline characteristics and 90-day outcomes. The two groups were overall similar with respect to age, median MELD-Na score and presence of organ failures at listing, though before the Share 35 rule, there were more patients listed with ACLF-3 listed who required mechanical ventilation (33.1% vs 27.7%, p=0.004). In the post-Share 35 era, 90-day waitlist outcomes improved among patients listed with ACLF-3, as the proportion who died decreased from 41.5% to 27.1% (p<0.001) and the percentage of candidates undergoing transplantation rose from 55.2% to 69.6% (p<0.001). Additionally, median waiting time to liver transplantation decreased from 6 to 4 days after implementation of the Share 35 rule (p<0.001).

These findings were corroborated with competing risks regression (Table S5, Figures 2a and 2b). After adjustment for variables including age and MELD-Na score, we

found that the post-Share 35 era was significantly associated with lower waitlist mortality (SHR=0.59, 95% CI 0.49-0.70), and greater likelihood of liver transplantation (SHR=1.56, 95% CI 1.38-1.76). This displayed in Table S5, columns 2 and 3. However, in a subgroup analysis of patients with 4-6 organ failures evaluating the outcome of 28-day waitlist mortality (Table S5, columns 4 and 5)), the Share 35 era was not associated with lower mortality (SHR=0.76, 95% CI 0.58-1.02) (figure 2c), though there was a significant association with increased probability of transplantation (SHR=1.38, 95% CI 1.06-1.80).

Post-transplant survival

Supplemental figure 4 shows the 1-year post liver transplantation survival of patients with 4-6 organ failures (n=358) compared to those with 3 organ failures (n=650). To ensure this cohort was representative of our study population at waitlist registration, the analysis was restricted to candidates with either 3 organ failures at both listing and liver transplantation or with 4-6 organ failures at listing and liver transplantation. The data show that the 1-year post liver transplantation survival of patients transplanted with 4-6 organ failures is 79.8% compared with 88.1% in those with 3 organ failures ($p<0.001$).

Discussion

As both the prevalence and mortality related to chronic liver disease is increasing, (17, 18) the burden of ACLF will rise over time, necessitating a better understanding of how to best approach organ allocation in these patients. In this regard, our investigation reveals several points that highlight the need for an alternative method to determine transplant priority among patients with severe ACLF, beyond the MELD-Na score. First, we demonstrate that patients with ACLF-3 but restricted to 3 organ failures still have greater mortality risk than candidates lower ACLF grades, despite having a similar likelihood for receiving liver transplantation. It is also notable that patients with three organ failures alone consisted predominantly of liver failure, renal failure and coagulation failure, whereas circulatory failure and need for mechanical ventilation were relatively absent.

Two important implications arise from this finding. First, the development of ACLF-3 yields a distinctly worse prognosis than determined by the MELD-Na score, even if all of the organ failures are accounted for in the MELD-Na score, through the measurement of serum bilirubin, creatinine, and international normalized ratio (INR). Subsequently, these patients may be disadvantaged by the current organ allocation rules as they have greater mortality risk, despite having similar likelihood for liver transplantation as candidates without ACLF-3. The reasons for this disparity may include physiologic alterations which occur in ACLF but not in acute decompensation, such as inflammatory cytokine release(19) and delayed clotting time(20), as well as the increased risk of bacterial infection in severe ACLF, which occurs independently of the MELD score.(21) Secondly, our analysis reveals that the majority of candidates with 3 organ failures alone (63.5%) had a combination of liver failure, renal failure and coagulation failure. However, these patients would not have been categorized as having ACLF without incorporation of liver and

coagulation failure. Therefore, there is prognostic value with the inclusion of intra-hepatic organ failures into the definition of ACLF, and reliance solely on the development of extra-hepatic organ failures may exclude certain patients at high risk of death.

In subgroup analysis, we further reveal that the discrepancies in waitlist outcomes among candidates with ACLF-3 are more pronounced with the presence of 4-6 organ failures. An analysis of data from the CANONIC study demonstrated the heterogeneity of patients designated as ACLF-3 by showing significantly greater mortality among those who have developed 4-6 organ failures versus those who have 3 organ failures.(16) Our study corroborates the higher mortality in patients with 4-6 organ failures, but further expands on this finding by highlighting that candidates with 4-6 organ failures also have lower likelihood for receiving liver transplantation. This may be due to a perception that post-transplant outcomes will be poor, despite recent evidence to the contrary both published in prior studies(22-24) and in our current investigation. Since implementation of the Share 35 rule in the United States, there has been a rise in the median MELD-Na score at liver transplantation and greater allocation to patients with MELD scores ≥ 35, including candidates with MELD-Na scores ≥ 40.(9, 10) Our study illustrates that the post-Share 35 era was associated with greater likelihood of transplantation among the entire cohort of ACLF-3 patients, including those with 4-6 organ failures. This finding is consistent with data from a prior study(9), and indicates more willingness to transplant patients with extra-hepatic organ failures since Share 35 implementation. However, implementation of the Share 35 era was not associated with reduced short-term mortality among patients with 4-6 organ failures despite greater transplant probability, suggesting that organ sharing policies centered around the MELD-Na score may not adequately reduce waitlist death in this population.

It is therefore interesting to consider whether additional priority for donor organs should be provided to patients with ACLF-3 or whether an alternate scoring system that incorporates organ failures should be applied to transplant candidates who fit this profile,(6) particularly since the sub-hazard ratio for mortality appears to be highest within the first week after listing. It is important to note, however, that although prioritizing patients with ACLF-3 would improve waitlist mortality, post-liver transplantation survival may decrease, particularly in recipients with circulatory failure, brain failure, or requiring mechanical ventilation at liver transplantation.(25) Therefore, an alternate proposal would be to allocate additional priority not simply based on the presence of ACLF-3, but rather after recovery of extra-hepatic organ system failures so that patients are transplanted in the appropriate window. Ultimately, although the data are compelling, our observations should be confirmed in a prospective study prior to implementing greater priority for patients with severe ACLF. Any suggested changes regarding distribution of donor organs should account for both improving waitlist mortality and also maximizing post-liver transplantation survival.

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, 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 though they had a decompensating event such as variceal bleeding or bacterial infection, which is not captured in the UNOS database. 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 lung injury that qualifies as respiratory failure may have not been intubated. Similarly, we cannot discern which patients had renal failure at listing due to chronic kidney disease. However, we attempted to address this limitation by conducting a sensitivity analysis. Thirdly, it is important to note that our study applies specifically to a population of patients listed for liver transplantation and the findings should not be extrapolated to predict non-transplant survival in the general population with ACLF. Furthermore, our study is restricted to patients with high MELD-Na scores at waitlist registration and the findings may not apply to candidates who develop ACLF and a MELD-Na score ≤ 35 after listing. Regarding our analysis of post-transplant survival among patients with 4-6 organ failures, the high survival rates we show are likely related to a selection bias due to transplanting the "fittest" patient. Therefore, our findings should not be extrapolated to all patients with 4 or more organ failures without accounting for factors such as sarcopenia or active infection. Finally, rules have recently been implemented in the United States to distribute organs based on distance from the donor hospital. It is possible that under this new policy, short-term waiting list mortality for ACLF-3 would be reduced. 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. Moreover, data regarding the high short-term waitlist mortality of ACLF-3 patients relative to candidates with similar MELD-Na scores but lower ACLF grades is valuable in guiding future research regarding optimizing organ distribution.

In conclusion, despite having equal priority for transplantation, patients with ACLF-3 have higher waitlist mortality relative to candidates with lower grades and similar MELD-Na scores. This is particularly the case for listed individuals with 4-6 organ failures, who not

only suffer from the greatest waitlist mortality but also the lowest likelihood for liver transplantation. Regional sharing has increased transplantation for patients with ACLF-3, including those with ≥ 4 organ failures, though waitlist mortality has not improved for this population after implementation of the Share 35 rule. Further investigation is needed to determine whether patients with ACLF-3 should be prioritized for transplantation using a scoring system that incorporates organ failures.

Figure legends

Figure 1a. Cumulative incidence function for mortality within 28 days of waitlist registration

Figure 1b. Cumulative incidence function for transplantation within 28 days of waitlist registration

Figure 2a. 90-day waitlist mortality among patients with ACLF-3 before and after share 35 rule implementation

Figure 2b. 90-day transplantation for patients with ACLF-3 before and after share 35 rule implementation

Figure 2c. 28-day waitlist mortality for patients with 4-6 organ failures before and after share 35 rule implementation

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Table 1. Patient characteristics at the time of waitlist registration and waitlist outcomes within 90 days, categorized by ACLF grade.

Recipient characteristics	**No ACLF (n=137)**	**ACLF-1 (n=560)**	**ACLF-2 (n=2,523)**	**ACLF-3 (n=3,122)**	**p-value***
Age, mean (SD)	46.6 (14.2)	54.7 (10.2)	52.1 (10.7)	52.1 (10.8)	<0.001
Male, n (%)	76 (55.5)	335 (59.8)	1,601 (63.4)	1,961 (62.8)	0.272
Race/ethnicity, n (%)					0.151
Caucasian	81 (59.1)	373 (66.6)	1,621 (64.3)	1,972 (63.2)	
African-American	24 (17.5)	59 (10.5)	304 (12.1)	388 (12.4)	
Hispanic	20 (14.6)	107 (19.1)	453 (17.9)	568 (18.2)	
Etiology, n (%)					0.005
NASH	12 (8.8)	119 (21.3)	434 (17.2)	459 (14.7)	
HCV	16 (11.7)	141 (25.2)	527 (20.1)	761 (24.4)	
ALD	33 (24.1)	220 (39.3)	877 (34.8)	1,095 (35.1)	
Cholestatic	20 (14.6)	47 (8.4)	287 (11.4)	264 (8.5)	
MELD score, median (IQR)	36 (35-38)	35 (34-37)	38 (36-40)	40 (38-40)	<0.001
MELD-Na score, median (IQR)	37 (36-38)	36 (36-37)	38 (37-40)	40 (39-40)	<0.001
Albumin, median (IQR)	2.9 (2.4-3.6)	3.2 (2.7-3.7)	3.1 (2.6-3.7)	3.2 (2.7-3.7)	<0.001
Bilirubin, median (IQR)	11.7 (3.9-23.3)	8.6 (6.1-10.5)	23.2 (11.7-32.4)	24.9 (16.2-34.6)	<0.001
Creatinine, median (IQR)	1.2 (1.0-3.0)	4.0 (2.1-4.0)	3.9 (1.9-4.0)	4.0 (2.8-4.0)	<0.001
INR, median (IQR)	1.7 (1.4-3.9)	2.2 (2.0-2.4)	2.4 (1.9-3.3)	2.8 (2.4-3.6)	<0.001
Renal replacement therapy, n(%)	16 (11.7)	233 (41.6)	929 (36.8)	1,583 (50.7)	
Sodium, median (IQR)	135 (131-138)	133 (128-137)	135 (131-138)	137 (133-140)	<0.001
Liver failure, n (%)	90 (65.7)	66 (11.9)	1,869 (74.1)	2,751 (88.1)	<0.001
Mechanical ventilation, n (%)	0 (0)	0 (0)	0 (0)	925 (29.6)	<0.001
Circulatory failure, n (%)	9 (6.6)	0 (0)	29 (1.1)	1,204 (38.6)	<0.001
Coagulation failure, n (%)	76 (55.5)	72 (12.9)	1,158 (45.9)	2,248 (72.0)	<0.001
Neurologic failure, n (%)	0 (0)	2 (0.4)	114 (4.5)	1,526 (48.8)	<0.001
Renal failure, n (%)	39 (28.4)	420 (75.0)	1,876 (74.4)	2,888 (92.5)	<0.001
Number of organ failures (n,%):					
Three				2,213 (70.9)	
Four-six				909 (29.1)	
Outcomes					
Died within 28 days	13 (9.5)	101 (18.0)	402 (15.9)	950 (30.4)	<0.001
Died within 90 days	16 (11.7)	124 (22.1)	486 (19.3)	1,015 (32.5)	<0.001
Days from listing to death (median, IQR)	17.5 (9.5-24.5)	11 (6-21.5)	13 (6-22)	7 (4-14)	<0.001
Transplanted within 90 days	86 (62.8)	382 (68.2)	1,884 (74.7)	2,016 (64.6)	<0.001

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

Table 2. Competing risks analysis regarding the outcomes of 90-day mortality or LT

	Univariable analysis (90-day mortality) SHR (95% CI)	**Multivariable analysis (90-day mortality) SHR (95% CI)**	**Univariable analysis (90-day LT) SHR (95% CI)**	**Multivariable analysis (90-day LT) SHR (95% CI)**
ACLF grade	Reference: No ACLF or ACLF-1	Reference: No ACLF	Reference: No ACLF	Reference: No ACLF
ACLF-2	1.67 (1.03-2.72)	0.96 (0.76-1.16)	1.25 (1.14-1.37)	1.17 (1.04-1.31)
ACLF-3	3.16 (1.95-5.13)	1.41 (1.12-1.78)	1.06 (0.96-1.16)	0.94 (0.80-1.11)
Meld-Na score	1.11 (1.08-1.14)	1.05 (1.01-1.08)	1.02 (1.00-1.04)	1.01 (0.99-1.03)
Female		1.05 (0.94-1.19)		0.93 (0.87-1.01)
Age		1.02 (1.02-1.03)		0.99 (0.98-0.99)
Race/ethnicity		Reference: White		Reference: White
Black		0.96 (0.78-1.18)		0.98 (0.87-1.10)
Hispanic		0.98 (0.84-1.14)		1.03 (0.94-1.12)
Etiology of cirrhosis		Reference: HCV		Reference: HCV
ALD		0.90 (0.79-1.04)		1.10 (1.02 -1.19)
NASH		0.96 (0.81-1.11)		1.02 (0.93-1.13)
Region		Reference: Low median meld		
Medium median meld		1.22 (1.04-1.45)		0.76 (0.69-0.84)
High median meld		1.41 (1.11-1.53)		0.69 (0.64-0.76)

Table 3. Organ failures associated with 90-day waitlist mortality among patients listed with ACLF-3, evaluated by Fine and Gray's competing risks regression

	Univariable analysis SHR (95% CI)	**Multivariable analysis* SHR (95% CI)**
Liver failure	0.94 (0.77-1.13)	
Mechanical ventilation	1.89 (1.67-2.15)	1.98 (1.75-2.24)
Circulatory failure	1.64 (1.45-1.86)	1.71 (1.52-1.94)
Coagulation failure	0.92 (0.81-1.05)	
Renal failure	1.12 (0.88-1.44)	
Brain failure	1.14 (1.02-1.30)	1.16 (1.03-1.33)

* adjusted for age and MELD-Na score

Table 4. Subgroup analysis dividing ACLF-3 into 3 organ failures or 4-6 organ failures

	Univariable analysis (28-day mortality) SHR (95% CI)	**Multivariable analysis (28-day mortality) SHR (95% CI)**	**Univariable analysis (28-day LT) SHR (95% CI)**	**Multivariable analysis (28-day LT) SHR (95% CI)**
ACLF grade	Reference: ACLF 0-2	Reference: ACLF 0-2	Reference: ACLF 0-2	Reference: ACLF 0-2
ACLF-3 (3 OF)	1.51 (1.33-1.72)	1.40 (1.20-1.63)	0.96 (0.90-1.03)	1.01 (0.94-1.09)
ACLF-3 (4-6 OF)	3.05 (2.65-3.51)	3.01 (2.54-3.58)	0.61 (0.55-0.67)	0.61 (0.54-0.68)
Meld-Na score	1.07 (1.04-1.11)	1.08 (1.03-1.12)	1.02 (1.00-1.04)	1.02 (0.99-1.04)
Male		1.00 (0.89-1.15)		1.05 (0.88-1.13)
Age		1.03 (1.02-1.04)		0.99 (0.98-0.99)
Race/ethnicity		Reference: White		Reference: White
Black		0.91 (0.74-1.14)		0.98 (0.88-1.11)
Hispanic		1.04 (0.89-1.17)		1.03 (0.95-1.13)
Etiology of cirrhosis		Reference: HCV		Reference: HCV
ALD		0.92 (0.77-1.01)		1.10 (1.02-1.19)
NASH		0.97 (0.81-1.15)		1.02 (0.92-1.12)
Region		Reference: Low median meld		
Medium median meld		1.16 (0.97-1.38)		0.77 (0.71-0.85)
High median meld		1.17 (0.99 -1.38)		0.70 (0.65-0.77)

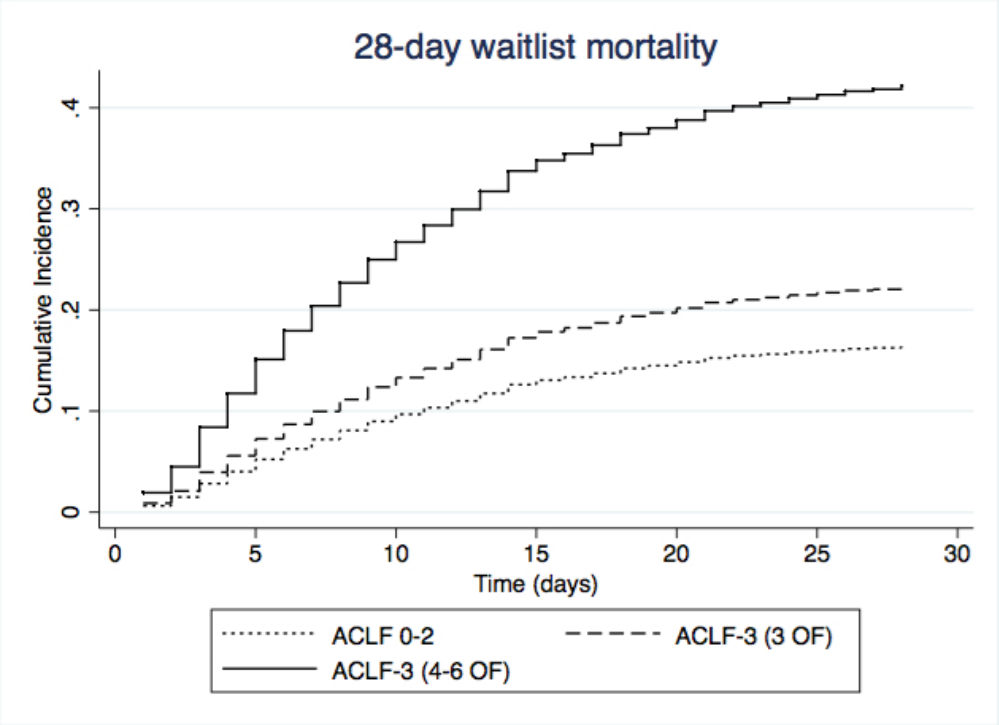


Figure 1a. Cumulative incidence function for mortality within 28 days of waitlist registration

53x38mm (300 x 300 DPI)

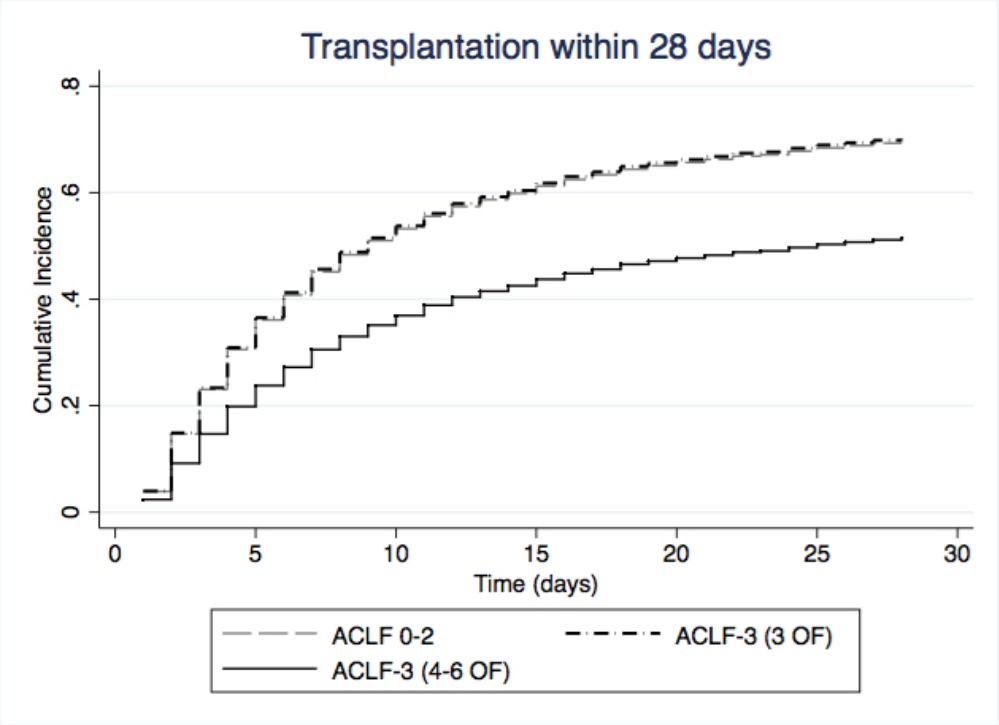


Figure 1b. Cumulative incidence function for transplantation within 28 days of waitlist registration

53x38mm (300 x 300 DPI)

Figure 2a. 90-day waitlist mortality among patients with ACLF-3 before and after share 35 rule implementation

53x38mm (300 x 300 DPI)

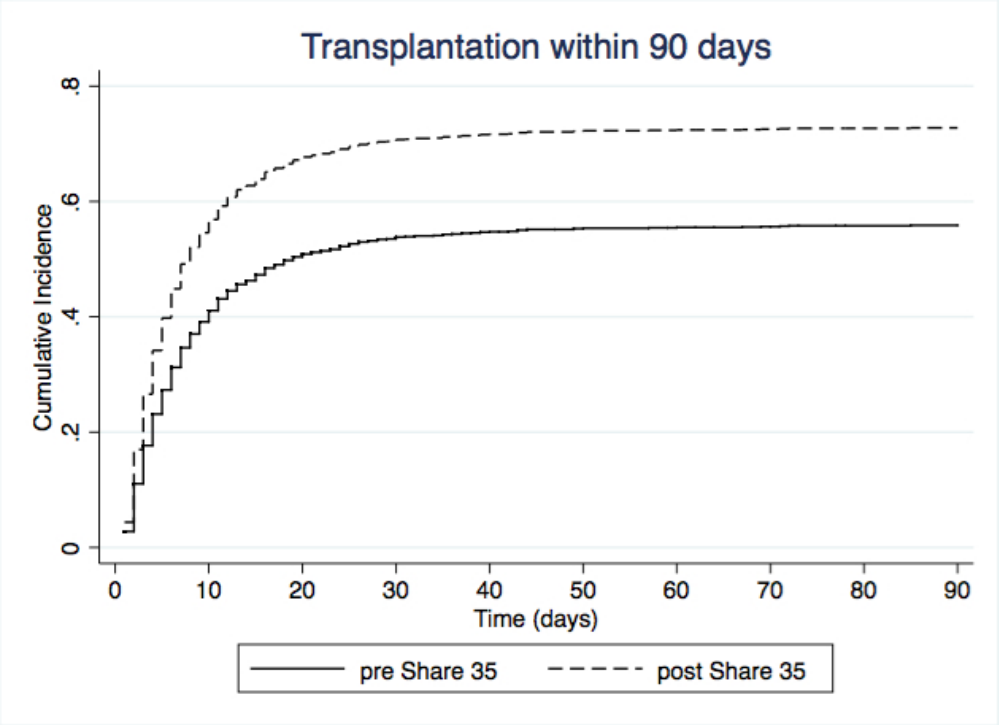


Figure 2b. 90-day transplantation for patients with ACLF-3 before and after share 35 rule implementation

53x38mm (300 x 300 DPI)

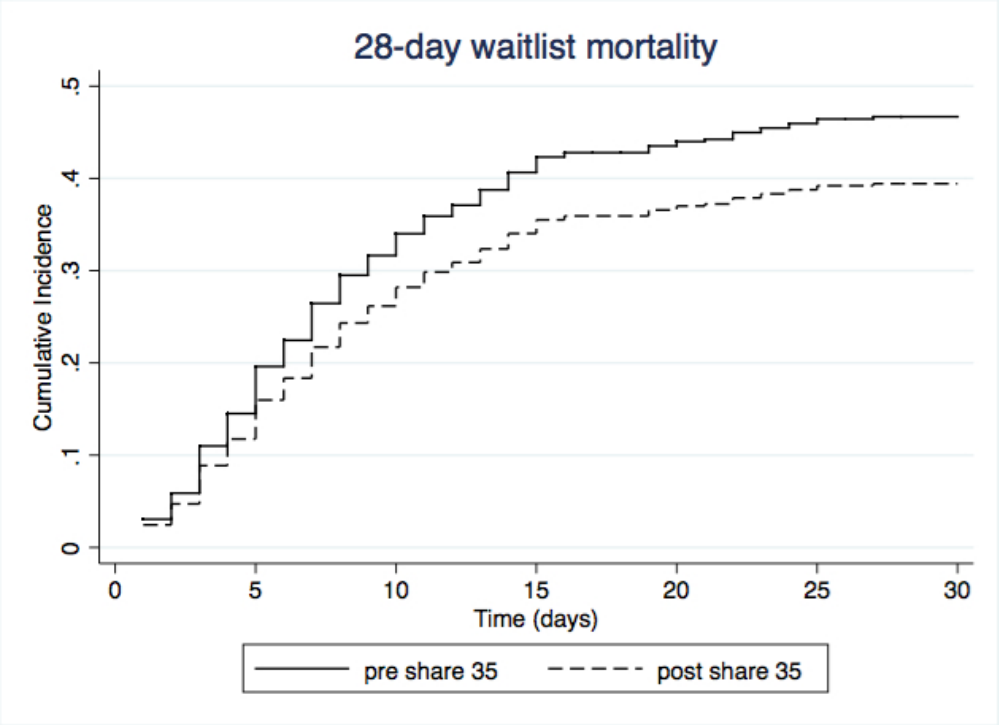


Figure 2c. 28-day waitlist mortality for patients with 4-6 organ failures before and after share 35 rule implementation

53x38mm (300 x 300 DPI)

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

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
Brain	grade 3-4 encephalopathy based on West-Haven criteria
Circulatory	requirement of vasopressors
Respiratory	requirement of mechanical ventilation
ACLF-1	• Single renal failure • Renal insufficiency with non-renal organ failure • Grade 1-2 encephalopathy based on West-Haven criteria with non-renal organ failure
ACLF-2	Two organ failures
ACLF-3	Three or more organ failures

Table S2. Patient characteristics with ACLF-3 comparing those who died or were transplanted within 90 days of listing

	Mortality within 90-days (n=1,015)	**Transplantation within 90 days (n=2,016)**	**p-value**
Age, mean (SD)	53.8 (10.3)	51.5 (10.7)	<0.001
Female, n (%)	387 (38.1)	737 (36.6)	0.398
MELD-Na, mean (SD)	39.1 (1.4)	39.1 (1.4)	0.276
Mechanical ventilation, n (%)	416 (40.9)	483 (23.9)	<0.001
Renal failure, n (%)	947 (93.4)	1,857 (92.1)	0.309
Circulatory failure, n (%)	490 (48.3)	678 (33.6)	<0.001
Liver failure, n (%)	890 (87.7)	1,794 (88.9)	0.288
Brain failure, n (%)	522 (51.4)	960 (47.6)	0.048
Coagulation failure, n (%)	713 (70.2)	1,479 (73.4)	0.070
Four to six organ failures:	411 (40.5)	478 (23.7)	<0.001

Table S3. Characteristics and short-term outcomes of ACLF-3 patients categorized by 3 organ system failures or 4-6 organ system failures

	Three organ failures (n=2,213)	**Four to six organ failures (n=909)**	**p-value**
Age, mean (SD)	52.3 (10.3)	51.7 (11.5)	0.249
Male, n (%)	1,442 (65.2)	518 (56.9)	<0.001
MELD-Na, median (IQR)	40 (39-40)	40 (38-40)	0.614
Total bilirubin, median (IQR)	25.6 (16.5-35.4)	23.7 (15.3-33.1)	
Creatinine, median (IQR)	4.0 (2.6-4.0)	4.0 (4.0-4.0)	
INR, median (IQR)	2.9 (2.5-3.6)	2.5 (2.0-3.4)	
Etiology: HCV ALD NASH	 552 (24.9) 811 (36.7) 331 (14.9)	 209 (22.9) 284 (31.2) 128 (14.1)	 0.143 <0.001 0.530
Mechanical ventilation, n (%)	45 (2.1)	880 (96.9)	<0.001
Renal failure, n (%)	2,042 (92.3)	846 (93.1)	0.501
Circulatory failure, n (%)	295 (13.3)	909 (100.0)	<0.001
Liver failure, n (%)	1,979 (89.4)	772 (84.8)	<0.001
Brain failure, n (%)	968 (43.7)	558 (61.4)	<0.001
Coagulation failure, n (%)	1,760 (79.5)	488 (53.7)	<0.001
Death within 28 days, n (%)	559 (25.3)	391 (43.0)	<0.001
Transplantation within 28 days, n (%)	1,538 (69.5)	478 (52.6)	<0.001

Table S4. Characteristics at listing and 90-day outcomes of patients listed with ACLF-3, categorized according to before or after share 35 era

	Pre-share 35 (n=994)	**Post-share 35 (n=1,321)**	**p-value**
Age, mean (SD)	52.3 (10.5)	52.7 (10.8)	0.249
MELD-Na, median (IQR)	40 (38-40)	40 (39-40)	0.195
Mechanical ventilation, n (%)	329 (33.1)	365 (27.7)	0.004
Renal failure, n (%)	914 (91.9)	1,233 (93.3)	0.223
Circulatory failure, n (%)	376 (37.9)	517 (39.1)	0.592
Liver failure, n (%)	881 (88.6)	1,158 (87.6)	0.539
Neurologic failure, n (%)	498 (50.1)	614 (46.5)	0.078
Coagulation failure, n (%)	176 (72.0)	956 (72.4)	0.836
Transplantation within 90 days, n (%)	549 (55.2)	919 (69.6)	<0.001
Death within 90 days, n (%)	413 (41.5)	364 (27.1)	<0.001
Waiting time if transplanted	6 (3-11)	4 (2-8)	<0.001

Table S5. Competing risks regression for 90-day waitlist outcomes among patients with ACLF-3 based on Share 35 era

	Multivariable* analysis (90-day mortality) SHR (95% CI)	**Multivariable* analysis (90-day transplantation) SHR (95% CI)**	**Multivariable** analysis (28-day mortality) SHR (95% CI)**	**Multivariable** analysis (28-day transplantation) SHR (95% CI)**
Share 35 era	0.59 (0.49-0.70)	1.56 (1.38-1.76)	0.76 (0.58-1.02)	1.38 (1.06-1.80)
Meld-Na score	1.04 (0.98-1.11)	1.01 (0.97-1.06)	1.02 (0.92 -1.12)	1.02 (0.93-1.11)
Male	1.09 (0.86-1.37)	1.15 (1.02-1.30)	0.97 (0.73-1.30)	1.11 (0.91-1.30)
Age	1.02 (1.01-1.03)	0.98 (0.98-0.99)	1.02 (1.00-1.03)	0.98 (0.97-0.99)
Race/ethnicity	Reference: White	Reference: White	Reference: White	Reference: White
Black	0.85 (0.62-1.14)	0.98 (0.86-1.12)	0.71 (0.44-1.15)	1.21 (0.80-1.82)
Hispanic	0.94 (0.75-1.16)	0.98 (0.86-1.13)	1.07 (0.76-1.47)	0.94 (0.68-1.29)
Etiology of cirrhosis	Reference: HCV	Reference: HCV	Reference: HCV	Reference: HCV
ALD	1.06 (0.87-1.28)	0.96 (0.84 -1.09)	0.79 (0.57-1.11)	1.26 (0.95 -1.68)
NASH	1.09 (0.79-1.51)	0.99 (0.83-1.17)	1.08 (0.74-1.59)	0.99 (0.67-1.47)
Region	Reference: Low median meld	Reference: Low median meld	Reference: Low median meld	Reference: Low median meld
Medium median meld	1.35 (1.05 -1.74)	0.72 (0.62-0.84)	1.19 (0.77-1.85)	0.71 (0.49-1.03)
High median meld	1.44 (1.13-1.83)	0.67 (0.58-0.77)	0.92 (0.60-1.39)	0.93 (0.66-1.31)

*Analysis of full cohort of patients listed with ACLF-3

** Analysis of patients with ACLF-3 and 4-6 organ failures

Figure S1. Flowchart for final study population

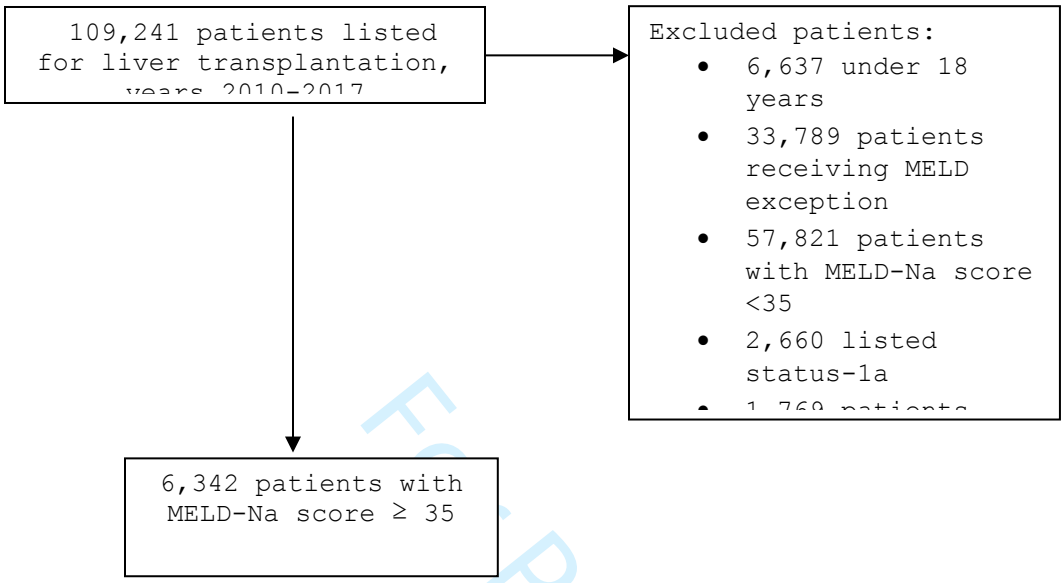


Figure S2. CIF for mortality within 90 days of waitlist registration

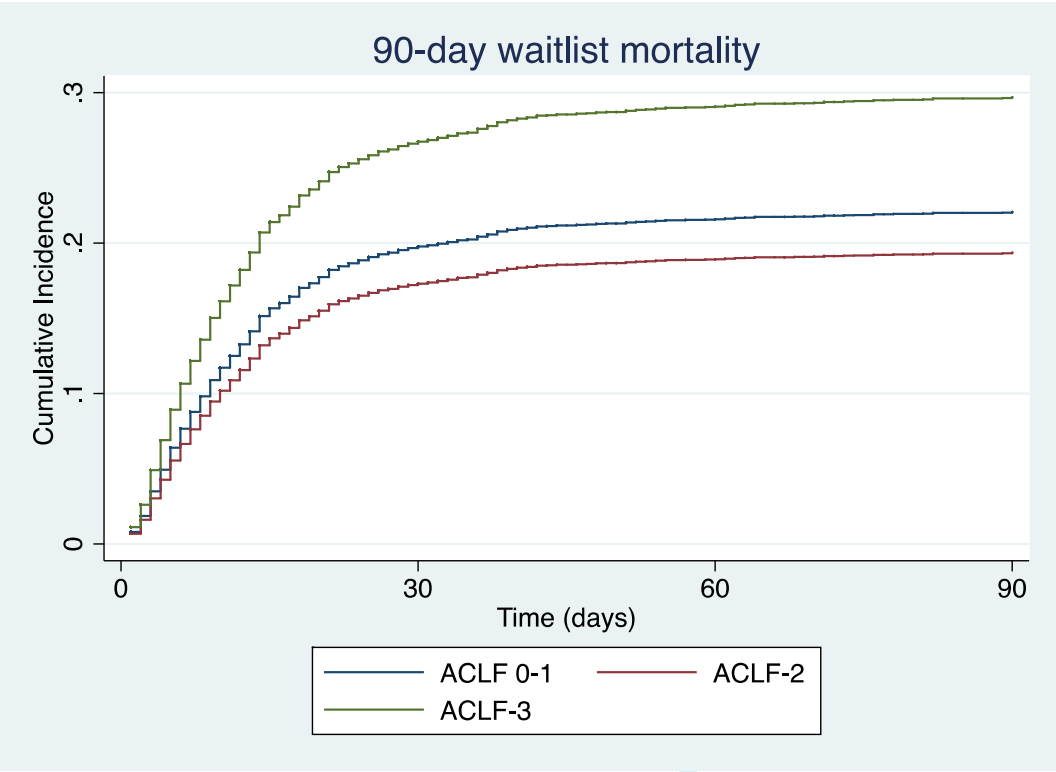


Figure S3. CIF for transplantation within 90 days of waitlist registration

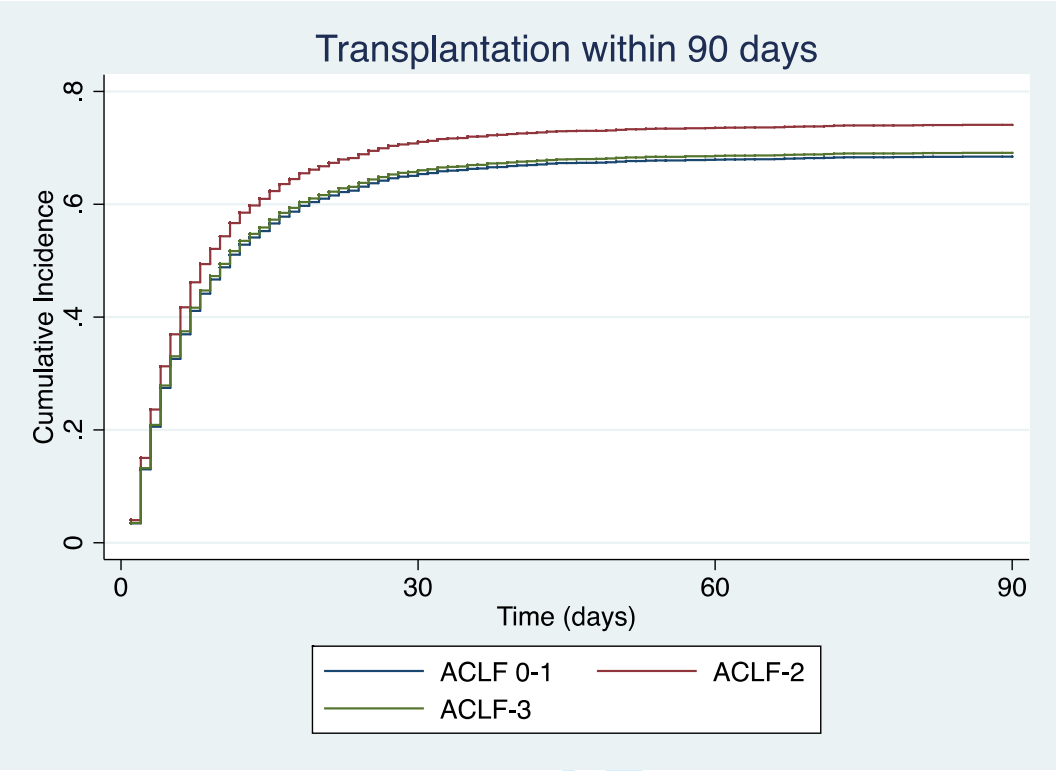
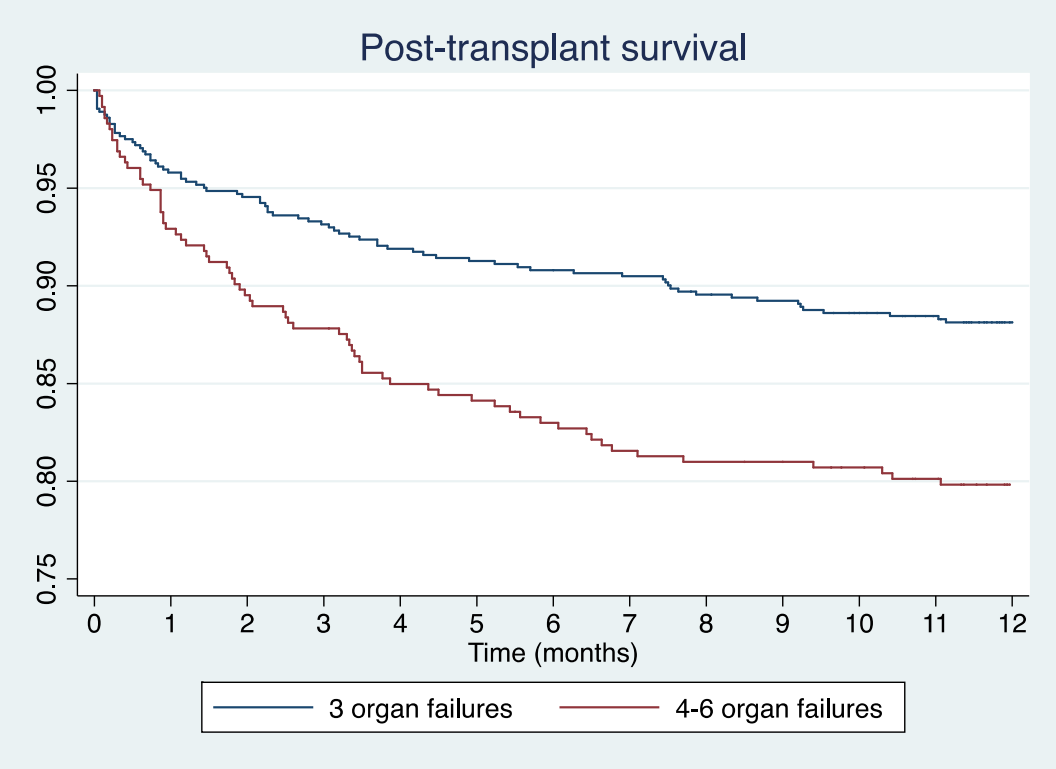


Figure S4. 1-year post transplant survival among patients with 3 or 4-6 OF at transplantation (p<0.001)



	1 month	3 months	6 months	12 months
3 organ failures	0.958 (0.939-0.971)	0.931 (0.909-0.949)	0.908 (0.883-0.928)	0.881 (0.854-0.904)
4-6 organ failures	0.929 (0.897-0.952)	0.878 (0.839-0.908)	0.829 (0.786-0.865)	0.798 (0.752-0.837)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – page 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – page 4
Objectives	3	State specific objectives, including any prespecified hypotheses – pages 4-5
Methods		
Study design	4	Present key elements of study design early in the paper – page 6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – page 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – page 6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – pages 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – page 6
Bias	9	Describe any efforts to address potential sources of bias – pages 7-8
Study size	10	Explain how the study size was arrived at – Figure S1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – pages 7-8
		(*b*) Describe any methods used to examine subgroups and interactions – page 7
		(*c*) Explain how missing data were addressed – pages 7-

	8
	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	(e) Describe any sensitivity analyses – page 10

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – Figure S1
		(b) Give reasons for non-participation at each stage – Figure S1
		(c) Consider use of a flow diagram – Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – page 10
		(b) Indicate number of participants with missing data for each variable of interest – page 9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) – page 10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time – Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – pages 10-15
		(*b*) Report category boundaries when continuous variables were categorized – table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – Tables 2-4
Discussion		
Key results	18	Summarise key results with reference to study objectives – page 16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – page 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – pages 16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results – page 19
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – page 1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.