

# Early transplantation maximizes survival in severe acute-on-chronic liver failure: Results of a Markov decision process model

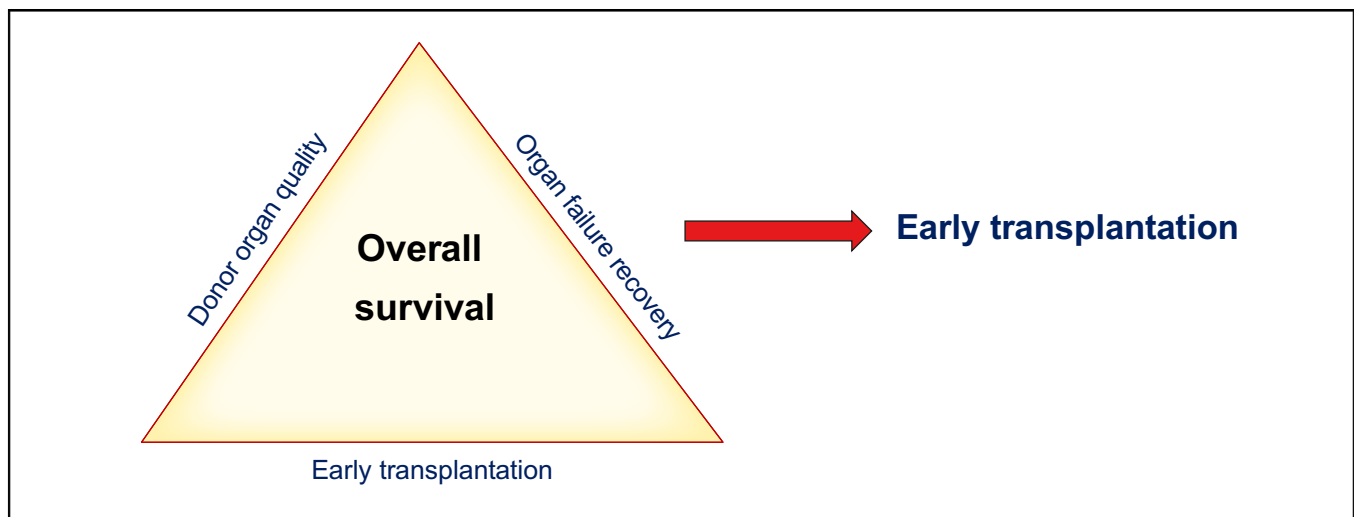
## Authors

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## Graphical abstract



## Highlights

- We created a Markov decision process model to maximize overall survival ACLF-3 patients within 7 days of listing.
- We examined three variables: earlier transplantation, organ quality, and recovery of organ failures.
- Earlier transplantation maximizes overall survival probability, due to high waitlist mortality of patients with ACLF-3.
- The impact of a marginal organ on post-LT mortality is less consequential than the mortality from delaying transplantation.
- The likelihood of organ failure recovery within 7 days of listing was less than 10%.

## Lay summary

In the setting of grade 3 acute-on-chronic liver failure (ACLF-3), questions remain regarding the timing of transplantation in terms of whether to proceed with liver transplantation with a marginal donor organ or to wait for an optimal liver, and whether to transplant a patient with ACLF-3 or wait until improvement to ACLF-2. In this study, we used a Markov decision process model to demonstrate that earlier transplantation of patients listed with ACLF-3 maximizes overall survival, as opposed to waiting for an optimal donor organ or for improvement in the number of organ failures.

# Early transplantation maximizes survival in severe acute-on-chronic liver failure: Results of a Markov decision process model



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**Background & Aims:** Uncertainties exist surrounding the timing of liver transplantation (LT) among patients with acute-on-chronic liver failure grade 3 (ACLF-3), regarding whether to accept a marginal quality donor organ to allow for earlier LT or wait for either an optimal organ offer or improvement in the number of organ failures, in order to increase post-LT survival. **Methods:** We created a Markov decision process model to determine the optimal timing of LT among patients with ACLF-3 within 7 days of listing, to maximize overall 1-year survival probability.

**Results:** We analyzed 6 groups of candidates with ACLF-3: patients age  $\leq 60$  or  $>60$  years, patients with 3 organ failures alone or 4-6 organ failures, and hepatic or extrahepatic ACLF-3. Among all groups, LT yielded significantly greater overall survival probability vs. remaining on the waiting list for even 1 additional day ( $p < 0.001$ ), regardless of organ quality. Creation of 2-way sensitivity analyses, with variation in the probability of receiving an optimal organ and expected post-transplant mortality, indicated that overall survival is maximized by earlier LT, particularly among candidates  $>60$  years old or with 4-6 organ failures. The probability of improvement from ACLF-3 to ACLF-2 does not influence these recommendations, as the likelihood of organ recovery was less than 10%.

**Conclusion:** During the first week after listing for patients with ACLF-3, earlier LT in general is favored over waiting for an optimal quality donor organ or for recovery of organ failures, with the understanding that the analysis is limited to consideration of only these 3 variables.

**Lay summary:** In the setting of grade 3 acute-on-chronic liver failure (ACLF-3), questions remain regarding the timing of transplantation in terms of whether to proceed with liver transplantation with a marginal donor organ or to wait for an optimal liver, and whether to transplant a patient with ACLF-3 or wait until improvement to ACLF-2. In this study, we used a Markov decision process model to demonstrate that earlier transplantation of patients listed with ACLF-3 maximizes overall survival, as opposed to waiting for an optimal donor organ or for improvement in the number of organ failures.

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## Introduction

Acute-on-chronic liver failure (ACLF) is an increasingly prevalent syndrome,<sup>1</sup> occurring in patients with decompensated cirrhosis, that is associated with severe systemic inflammation,<sup>2-4</sup> organ failures, and high 28-day mortality.<sup>5</sup> The short-term mortality of certain patients with ACLF grade 3 (ACLF-3), defined as the development of  $\geq 3$  organ failures,<sup>5</sup> is particularly high<sup>6-8</sup> and potentially surpasses that of acute liver failure.<sup>9</sup> Mortality is especially great for those with 4-6 organ failures who have been

shown to have a 100% mortality within 28-days from presentation, as demonstrated by a prospective study.<sup>10</sup> Liver transplantation (LT) yields excellent patient survival both at 1-year and in the long-term.<sup>11,12</sup> However, uncertainty still remains regarding the appropriate timing of transplantation in this population, due to challenges related to waitlist and post-transplant mortality.

There are several factors which may be incorporated into the timing of transplanting a patient with ACLF-3, including the likelihood of dying on the waiting list if LT is delayed, the potential for recovery of organ failures prior to transplantation to improve post-transplant survival, and the greater post-transplant mortality associated with utilizing a marginal quality organ. A prior registry study demonstrated that the occurrence of LT within 30 days in patients listed with ACLF-3 was

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associated with reduced 1-year post-LT mortality, but also demonstrated that transplantation using an organ with a donor risk index (DRI)  $\geq 1.7$  predicted greater likelihood of death after LT.<sup>11</sup> Additionally, though earlier transplantation in patients with ACLF-3 may improve post-LT survival, greater post-LT survival may be achieved by transplanting the patient after organ failure improvement and subsequent recovery from ACLF-3, particularly in patients  $>60$  years.<sup>13</sup>

To address these uncertainties surrounding LT in patients with ACLF-3, we created a Markov decision process model which maximizes overall survival probability, accounting for expected waitlist mortality, post-transplant survival based on donor organ quality, and likelihood of organ failure recovery prior to transplantation. We hypothesized that due to the high waitlist mortality associated with ACLF-3, earlier transplantation of candidates listed with ACLF-3 yields the greatest survival probability, even when accounting for reduced post-LT survival with a marginal quality organs<sup>11</sup> and increased post-LT survival associated with organ failure recovery prior to transplantation.<sup>13</sup>

## Patients and methods

The study protocol was considered exempt from review by the institutional review board at Cedars-Sinai Medical Center. The study and analysis of this study was performed in accordance with STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) guidelines.<sup>14</sup>

### United Network for Organ Sharing (UNOS) database analysis

From the UNOS registry ([www.unos.org](http://www.unos.org)), we evaluated patients aged 18 or older listed for LT from 2005 to 2017. Patients who were listed as status-1a, who were retransplanted or who underwent multi-organ transplantation, aside from simultaneous liver and kidney transplantation, were excluded. We collected data regarding patient characteristics at the time of waitlist registration, as well as information regarding waitlist outcomes and post-LT outcomes.

### Identification of patients with ACLF

ACLF at the time of waitlist registration was identified based on the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) criteria of having a single 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 2 non-renal organ failures.<sup>5</sup> (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 failure score for coagulopathy, liver failure, renal dysfunction and renal failure, neurologic failure, and circulatory failure.<sup>5</sup> 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 transplantation. (Table S1) This methodology has been utilized in several previously published studies regarding LT related to ACLF.<sup>4,9,11</sup> All patients analyzed had ACLF-3 at the time of listing and at transplantation.

We categorized organ quality as optimal (DRI  $<1.7$ ) or marginal (DRI  $\geq 1.7$ ).<sup>15</sup>

### Overview of model creation

We used a stochastic dynamic programming model, which considers the risk of death over time without transplantation, post-LT survival, and uncertainty in quality of livers offered for transplantation in the future, to evaluate the optimal time to accept a liver allograft for LT. The Markov decision process model captures the likelihood of death or being offered an optimal organ daily, for 7 days from the time of listing. We chose a time horizon of 7 days to minimize the chance of daily variation in the patient's course and because non-transplant mortality approached 50% by day 7, per our analysis. On each of the first 7 days after listing, the provider may accept the organ, upon which the model calculates the 1-year post-transplant survival. If the provider declines the organ, the model resets and the provider will be offered either an optimal or marginal liver the next day. In our Markov decision process model, we accounted for the following factors: patient age  $>$  or  $\leq 60$  years,<sup>13</sup> number of organ failures at listing (3 vs. 4-6), organ quality, and waiting time until LT.

### Model assumptions

We made several assumptions in the model. First, we assumed that each day, a liver of either optimal or marginal quality will be provided to each patient who has not been transplanted and that a marginal liver results in a lower 1-year post-LT survival probability. Secondly, we assumed that the probability of being offered an optimal organ is constant and independent of the organ quality offered the previous day. Finally, we assumed that best strategy is to always accept an optimal organ if one is offered.

### Details of Markov model

We modeled the likelihood of receiving an optimal organ each day as  $\alpha$ , and the likelihood of receiving a marginal organ as  $1-\alpha$ . Because the probability of receiving an organ offer varies across UNOS regions, we examined different values of  $\alpha$ . For instance, if a center has an expected 70% probability of a liver offer, then  $\alpha$  would be 0.7. (Fig. 1) We utilized 2 Markov processes: the pre-transplant process (Fig. 1, top box) and the post-transplant process (Fig. 1, bottom box). On each day  $t$  after listing, the candidate has a non-transplant mortality probability of  $\gamma_t$ , as determined from the UNOS database.

### Timing of organ acceptance and relative risk

To find the optimal time to accept a marginal organ, we used a backwards induction algorithm<sup>16,17</sup> designed to maximize expected 1-year survival, given all possible decisions on each day (supplemental appendix, section 1). Length of hospital stay does not differ substantially between patients with earlier or later transplants, and we therefore omitted this consideration from our analysis. The difference in post-LT survival probability when transplanted with a marginal vs. optimal organ was estimated by the relative risk (Fig. S1). In our base case analysis, we used 0.9 as the relative risk, but we varied the relative risk from 0.6 to 0.9 in sensitivity analyses (Fig. S1).

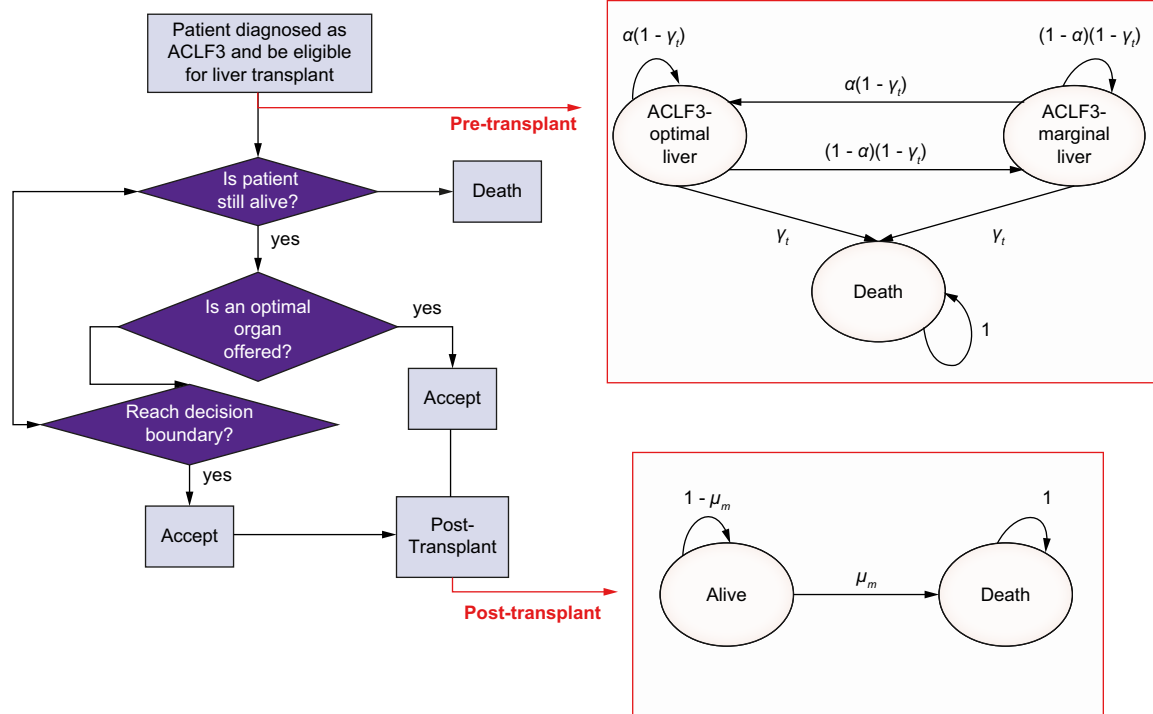


Fig. 1. Diagram of patient flow while awaiting liver transplantation. ACLF-3, acute-on-chronic liver failure grade 3.

**Outcome metrics**

Our primary outcome was which day the provider should stop waiting for an optimal organ and accept a marginal liver. Because of variation in organ availability and post-transplant outcomes between centers, we presented our results across different parameter values. Our results are therefore presented across multiple values of the probability an optimal organ is offered ( $\alpha$ ) and the relative risk of survival for a marginal organ (relative

risk) in 2-way graphs. Exact equations and details for both can be found in the [supplementary information](#).

**Statistical analysis**

Data was extracted and analyzed from the UNOS database using Stata 16 (Houston, TX), with descriptive statistics performed with analysis of variance with Bonferroni correction for continuous variables and Chi-square testing for categorical variables. Survival

Table 1. Baseline characteristics of the study population with ACLF-3 at time of waitlist registration.

	Age ≤60 years (n = 4,359)	Age >60 years (n = 1,492)	p value	3 organ failures (n = 4,035)	4-6 organ failures (n = 1,816)	p value
Age, (SD)	47.6 (9.2)	63.8 (3.2)	<0.001	51.8 (10.3)	50.3 (11.6)	0.002
Male (%)	2,721 (62.4)	872 (58.5)	<0.001	2,558 (63.4)	1,035 (56.9)	<0.001
Race/ethnicity (%):			<0.001			0.001
Caucasian	2,795 (64.1)	980 (65.7)		2,671 (66.2)	1,104 (60.8)	
African American	540 (12.4)	170 (11.4)		481 (11.9)	229 (12.6)	
Hispanic	752 (17.3)	240 (16.1)		647 (16.0)	345 (19.0)	
Missing	88 (1.9)	14 (0.9)		64 (1.6)	32 (1.8)	
Etiology of liver disease (%):			<0.001			<0.001
Alcohol	1,408 (32.3)	373 (25.0)		1,278 (31.7)	472 (25.9)	
NAFLD	444 (10.2)	289 (19.4)		528 (13.1)	205 (11.3)	
Hepatitis C virus	1,163 (26.7)	199 (13.3)		1,101 (27.3)	435 (23.9)	
Hepatitis B virus	233 (5.4)	66 (4.4)		198 (4.9)	101 (5.6)	
Autoimmune hepatitis	232 (5.3)	80 (5.4)		213 (5.3)	99 (5.5)	
Primary biliary cholangitis	85 (1.9)	55 (3.7)		93 (2.3)	47 (2.6)	
Primary sclerosing cholangitis	86 (1.9)	26 (2.4)		93 (2.3)	29 (1.6)	
Cryptogenic	230 (5.3)	192 (10.2)		259 (6.4)	123 (6.8)	
Other	478 (10.9)	212 (14.2)		272 (6.7)	305 (16.8)	
MELD-Na score, (SD)	39.1 (6.4)	38.4 (7.0)	0.001	38.5 (6.3)	39.1 (6.7)	0.047
Liver failure (%)	3,605 (82.8)	1,141 (76.5)	<0.001	3,329 (82.5)	1,421 (78.3)	<0.001
Renal failure (%)	3,487 (80.1)	1,243 (83.3)	0.005	3,247 (80.5)	1,483 (81.7)	0.284
Coagulation failure (%)	2,856 (65.5)	916 (61.4)	0.004	2,872 (71.2)	900 (49.6)	<0.001
Brain failure (%)	2,344 (53.8)	819 (54.9)	0.463	2,006 (49.7)	1,158 (63.8)	<0.001
Circulatory failure (%)	1,924 (44.1)	729 (48.3)	0.006	828 (20.5)	1,802 (99.2)	<0.001
Mechanical ventilation (%)	1,647 (37.8)	616 (41.3)	0.016	478 (11.9)	1,785 (98.3)	<0.001

Statistical analysis performed using Analysis of Variance for continuous variables and Chi-square analysis for categorical variables. ACLF-3, acute-on-chronic liver failure grade 3; MELD-Na, model for end-stage liver disease-Na; NAFLD, non-alcoholic fatty liver disease.

analyses were assessed using Kaplan-Meier methods, with log-rank testing. The Markov decision process model was created using Python 3.6.

## Results

### Patient characteristics, categorized by age group and number of organ failures

Baseline characteristics of the study population are depicted in Table 1. We identified 5,851 patients listed with ACLF-3 who met our inclusion and exclusion criteria, representing 4.3% of the 134,728 patients listed for LT. Patients were subdivided according to age above or  $\leq 60$  years or the presence of 3 or 4-6 organ failures at waitlist registration. We did not create additional stratifications within these subgroups, such as patients above age 60 and with 4-6 organ failures, due to loss of sample size.

When classifying the transplant candidates according to the number of organ system failures at listing, we identified 4,035 (68.9%) patients with 3 organ failures and 1,816 (31.1%) patients with 4-6 organ failures. Mean model for end-stage liver disease (MELD)-Na score at listing was higher among patients listed with 4-6 organ failures (39.1 vs. 38.5,  $p = 0.047$ ). Additionally, patients with 4-6 organ failures had a greater prevalence of brain failure

(63.8% vs. 49.7%,  $p < 0.001$ ), circulatory failure (99.2% vs. 20.5%,  $p < 0.001$ ) and need for mechanical ventilation (98.3% vs. 11.9%), while those with only 3 organ failures had a higher prevalence of liver failure (82.5% vs. 78.3%,  $p < 0.001$ ) and coagulation failure (71.2% vs. 49.6%,  $p < 0.001$ ).

### Non-transplant survival probability

Non-transplant survival probabilities are depicted in Fig. S2. By the seventh day, the survival probability is 60.3% for patients aged  $\leq 60$  and 52.8% for patients aged  $> 60$  years ( $p = 0.009$ ). When examining of 3 vs. 4-6 organ failures, we found that by day 7, the survival probability was 62.7% for patients with 3 organ failures and 51.8% for patients with 4-6 organ failures ( $p = 0.009$ ).

### Post-transplant survival probability

One-year post-LT survival probabilities are displayed in Fig. S3. In Fig. S3A, survival after LT is depicted according to age and donor organ quality. Among patients younger than 60 years the 1-year survival probability is 86.2% when transplanted with a low DRI liver and 78.2% using a high DRI organ. Among recipients  $> 60$  years old, 1-year survival after LT was 77.1% using an optimal liver and 74.1% with a marginal liver. Fig. S3B shows similar post-LT survival, categorized by number of organ failures

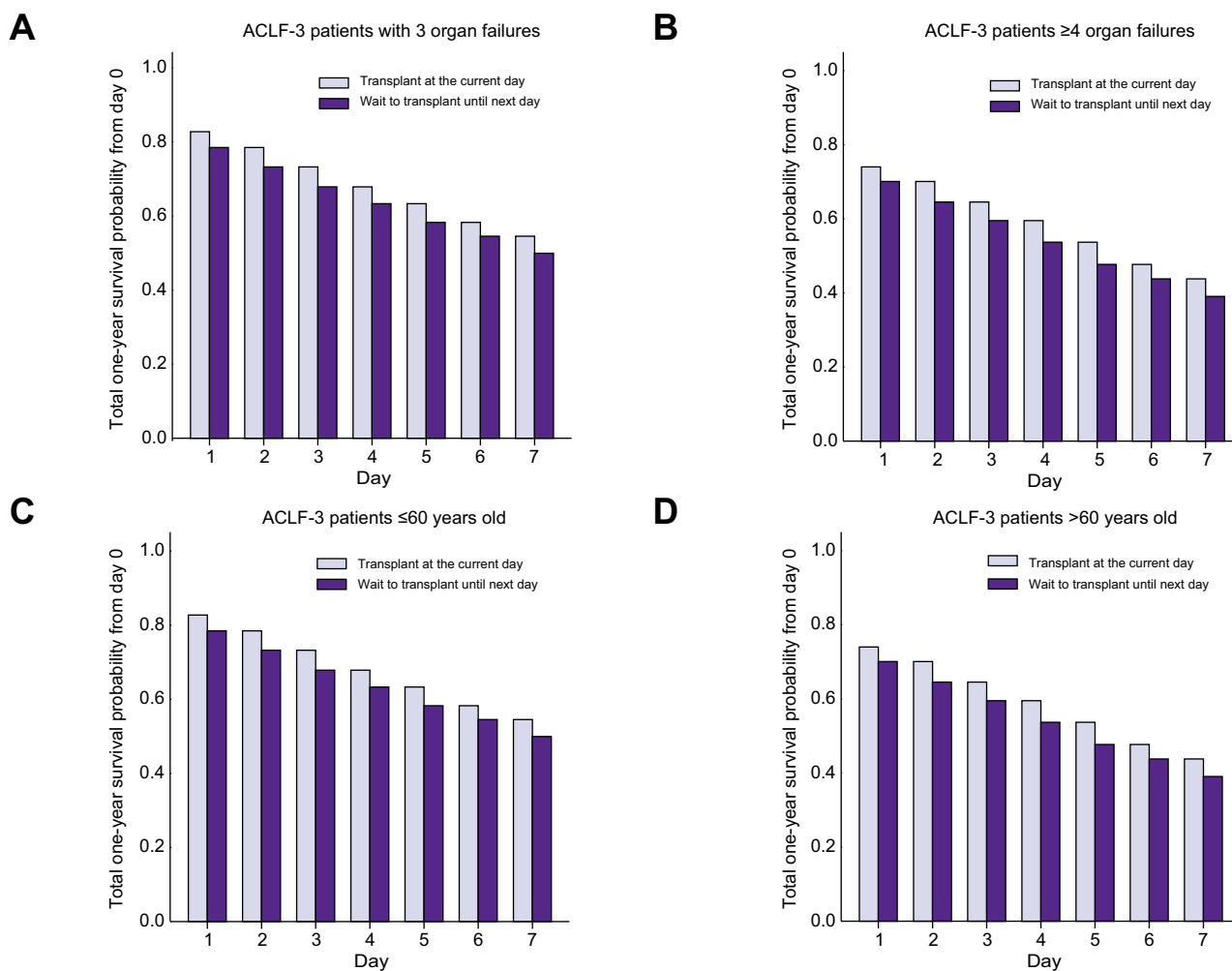


Fig. 2. Overall, 1-year survival probability based on the decision to transplant on a specific day or defer LT for 1 day. ACLF-3, acute-on-chronic liver failure grade 3; LT, liver transplantation.

**Table 2. Model parameters and sources, including pre- and post-transplant survival probabilities, relative risk of post-LT mortality and health-related utility values.**

Variable	Value
<b>ACLF-3 patients non-transplant survival probabilities (<math>1-\gamma_t</math>), by age and day (1-7):</b>	
>60 years old	
Day 1	0.9468
Day 2	0.8719
Day 3	0.8042
Day 4	0.7252
Day 5	0.6442
Day 6	0.5916
Day 7	0.5275
≤60 years old,	
Day 1	0.9485
Day 2	0.8850
Day 3	0.8201
Day 4	0.7650
Day 5	0.7040
Day 6	0.6590
Day 7	0.6032
<b>ACLF-3 patients post-transplant survival probabilities (<math>1-\mu_{12}</math>) transplanted in the first week:</b>	
Optimal Liver	
>60 years old, 12 months post-transplant	0.7709
≤60 years old, 12 months post-transplant	0.8618
Marginal Liver	
>60 years old, 12 months post-transplant	0.7407
≤60 years old, 12 months post-transplant	0.7819
<b>ACLF-3 patients non-transplant survival probabilities (<math>1-\gamma_t</math>), by organ failures and Day (1-7):</b>	
>3 organ failures	
Day 1	0.9336
Day 2	0.8501
Day 3	0.7745
Day 4	0.7064
Day 5	0.6289
Day 6	0.5806
Day 7	0.5183
=3 organ failures,	
Day 1	0.9575
Day 2	0.9024
Day 3	0.8433
Day 4	0.7868
Day 5	0.7283
Day 6	0.6823
Day 7	0.6274
<b>ACLF-3 patients post-transplant survival probabilities (<math>1-\mu_{12}</math>) transplanted in the first week:</b>	
Optimal liver	
>3 of, 12 months post-transplant	0.7922
=3 of, 12 months post-transplant	0.8654
Marginal liver	
>3 of, 12 months post-transplant	0.6963
=3 of, 12 months post-transplant	0.8030
Relative risk of post-transplant mortality between recipients of a marginal vs. an optimal liver	0.90 (varied in sensitivity analysis)
Daily probability of getting an optimal liver ( $\alpha$ )	0.6 (varied in sensitivity analysis)

Data sourced from the United Network for Organ Sharing. ACLF-3, acute-on-chronic liver failure grade 3; LT, liver transplantation.

at listing and the type of donor organ. When transplanted with an optimal liver, the 1-year survival probability is 86.5% for a patient with 3 organ failures vs. 80.3% with a marginal organ. Among patients with 4-6 organ system failures, the 1-year survival is 79.2% when using a low DRI organ and 69.6% after LT with a high DRI organ.

**Overall survival probability**

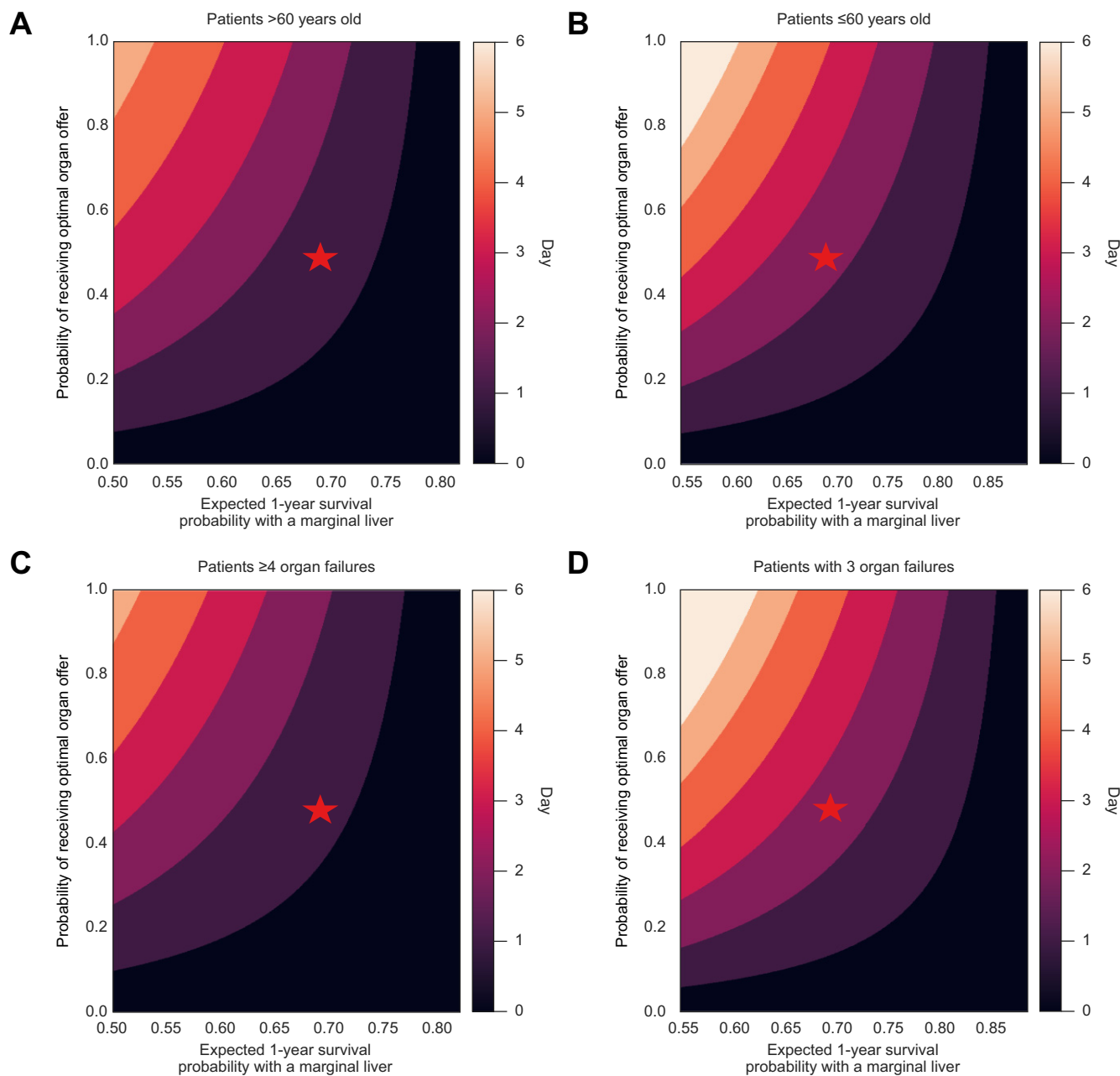
We next compared overall survival probability among the 4 patient subgroups (Fig. 2A-D), based upon whether the decision was made to proceed with transplantation on a specific day, regardless of organ quality, or to decline an organ offer and proceed with LT on the next day. The daily survival probabilities for each group, as based on these decisions, are provided in Table S2. In Fig. 2A, which depicts patients with 3 organ failures at listing, we demonstrate that from day 1 through 7 on the waiting list, LT yields a daily average of 4.4% greater overall survival probability than remaining on the waitlist for an additional day ( $p < 0.001$ ). Similar findings were demonstrated among patients with 4-6 organ failures at listing (Fig. 2B), with a 5.2% difference in overall survival from day 1-7 after listing ( $p < 0.001$ ). In Fig. 2C and 2D, survival probabilities are displayed among patients categorized according to age. For candidates aged ≤60 years, the average daily difference in overall survival was 4.7% ( $p < 0.001$ ), whereas for patients older than 60 years, the average difference in survival was 5.0% ( $p < 0.001$ ). These findings suggest that during the first week on the waiting list for patients with ACLF-3, a delay in LT by 1 day is associated with a reduction in overall survival probability.

**Timing of accepting a marginal quality donor organ: base case**

We created a Markov decision process model to address the timing of when to accept a marginal organ. Values for selected parameters including pre- and post-LT survival probabilities, likelihood of receiving an organ, and relative risk of post-transplant are listed in Table 2. For the base case, we estimated the relative risk of post-transplant survival between a marginal and optimal liver to be roughly 0.9 (equivalent to 0.78 probability of 1-year survival for a marginal liver compared to 0.86 for an optimal liver) based on analysis of the UNOS database. We assumed the likelihood of being offered an optimal liver to be 60% ( $\alpha = 0.6$ ). In this scenario, for a patient with 3 organ failures alone, if an optimal organ is not offered on day 1 and day 2, we recommend accepting a marginal liver starting on day 3 and proceeding with LT. However, if the patient has 4-6 organ failures at listing, we recommend accepting a marginal liver on day 1 of listing, regardless of the patient's age, due to the high non-transplant mortality associated with having 4-6 organ failures. The expected 1-year post-transplant survival probability is 79.8% for recipients with 3 organ failures and 71.3% for patients with 4-6 organ failures. For patients in both age groups, we recommend accepting a marginal liver on day 2 of listing. In this scenario, the expected 1-year post-transplant survival probability is 70.3% for patients >60 years and 78.7% for those ≤60 years old.

**Variation in the relative risk and probability of optimal organ offer**

As the probability of receiving an organ offer and the post-transplant survival utilizing a marginal liver differs between centers, we determined the timing regarding when to accept a marginal quality organ, using different probabilities of receiving an optimal liver offer, across variable post-LT survival probabilities when using a marginal liver. Fig. 3A-D display 2-way sensitivity analyses depicting the maximum number of days to wait for an optimal liver, based on the expected probability of receiving an offer and the expected post-transplant survival for each center. The y-axis represents the likelihood of receiving an optimal organ, ranging from 0 to 1. The x-axis represents the expected 1-year survival when transplanted with a marginal



**Fig. 3. Two-way sensitivity analyses, accounting for center variation regarding probability of receiving an optimal organ offer and expected 1-year post-LT survival using a marginal quality organ.** (A) We display a scenario of a transplant candidate >60 years old. With an expected one-year survival of 70% for patients transplanted with a marginal liver and 50% daily likelihood of being offered an optimal liver, LT should proceed on day 1 regardless of organ quality. (A, red star) However, if the patient is ≤60 years old, then LT can occur on day 2 or before regardless of organ quality. (B, red star) (C,D) Additional scenarios according to the presence of 3 or 4–6 organ failures at waitlist registration. LT, liver transplantation.

liver, which varies from 0.5 to 0.9. On the right side of each graph are the representative decision boundaries to determine which day after listing the provider should proceed with LT, even if offered a marginal organ.

In Fig. 3A, we display a scenario of a transplant candidate >60 years old. In this setting, if the center has an expected 1-year survival of 70% for patients transplanted with a marginal liver and a 50% daily likelihood of being offered an optimal liver, then LT should proceed on day 1 if an organ is offered, regardless of quality (Fig. 3A, red star). However, if the patient is ≤60 years old,

the center can wait until day 2 before accepting a marginal organ (Fig. 3B, red star). We describe additional scenarios according to the presence of 3 or 4–6 organ failures at waitlist registration in Fig. 3C,D. As expected, the decision boundaries occur earlier for patients aged >60 years or with 4–6 organ failures at listing, indicating survival benefit with shorter waiting time.

#### Hepatic vs. extrahepatic ACLF-3

We also examined outcomes for patients listed with ACLF-3 according to the presence or absence of extrahepatic organ failures,

with extrahepatic organ failures defined as either brain failure, circulatory failure, or need for mechanical ventilation. Although renal failure is also deemed an extrahepatic organ failure, for the purposes of this analysis we considered it as a hepatic failure. Our reasons for doing so were twofold. First, if we analyzed transplant candidates only with hepatic failures, specifically liver and coagulation failure, then these patients would be classified as ACLF-2 and not ACLF-3, which was the intended study population. Secondly, a prior study has demonstrated that the presence of brain failure, circulatory failure, or need for mechanical ventilation at LT negatively impacted post-transplant survival, whereas the development of renal failure at LT did not.<sup>13</sup> Survival probabilities are summarized in [Table S4](#). [Fig. S7](#) depicts the effect of variation in the relative risk and probability of an optimal organ offer. For instance, if the center has an expected 1-year survival of 70% for patients transplanted with a marginal liver and a 50% daily likelihood of being offered an optimal liver, then LT should proceed on day 1 if an organ is offered to a patient with hepatic ACLF-3, regardless of quality ([Fig. S7A](#), red star). However, if the patient has extrahepatic ACLF-3, the center can wait until day 2 before accepting a marginal organ ([Fig. S7B](#), red star).

### Improvement to ACLF-2

We then extended our model by considering improvement to ACLF-2 from listing to LT, which would subsequently improve pre- and post-transplant survival.<sup>13</sup> ([Fig. S4](#)) We restructured the model by introducing 2 new states: ACLF-2 with optimal organ offered and ACLF-2 with marginal organ offered, based on the assumption that a patient listed with ACLF-3 can improve in the number of organ failures on each day. The rest of the model structure remained the same. With this modification, we found that the optimal policy remains the same as in the base case, as the probability of improvement from ACLF-3 to ACLF-2 within the first week after listing is low (<10%) compared to the benefit of proceeding with transplantation ([Table S3](#)). Therefore, considering recovery to ACLF-2 did not change the strategy determined by our model.

### Sensitivity analyses

We performed 2 sensitivity analyses to test the robustness of our findings. In the first, we removed patients with suspected chronic kidney disease based on a previously validated methodology.<sup>18</sup> After removal of 582 patients with suspected chronic kidney disease (9.9%), we demonstrated similar decision boundaries across all 4 patient groups ([Fig. S5](#)). In the second analysis, we analyzed patients transplanted from year 2014 ( $n = 2,264$ ) to more accurately reflect the current epidemiological landscape of liver disease by evaluating the consistency of our findings in the post direct-acting antiviral era.<sup>19</sup> In this scenario, the decision boundary for patients with 4-6 organ failures increased, thereby allowing for a greater waiting period before recommending acceptance of a marginal organ. The decision boundaries for other groups remains the same ([Fig. S6](#)).

### Analysis of length of stay

Although our study was focused on the outcome of 1-year post-LT survival, we also performed analysis to determine if the day of transplantation impacted post-transplant length of hospital stay. Among the 4 patient groups studied, the day of transplantation did not significantly affect length of hospital stay after LT ([Table S5](#)).

## Discussion

Our study demonstrates that among the 3 competing variables of earlier transplantation, donor organ quality, and candidate organ failure recovery, it is earlier transplantation that leads to the greatest overall survival probability. This is due to the high non-transplant mortality after listing, the less consequential impact of organ quality on post-LT mortality, and the low likelihood of organ failure recovery within the first 7 days after listing. Our findings are particularly relevant to patients aged >60 or with 4-6 organ failures at listing, regardless of age, since these patient groups have the highest probability of non-transplant mortality. Mortality rates without LT were higher in our investigation than in prior prospective studies,<sup>10,20</sup> but we believe this is because we evaluated mortality from the time of listing for LT rather than the day of initial presentation with ACLF-3. Although our study provides guidance regarding which day to proceed with LT, we acknowledge that a variety of other factors beyond organ quality are incorporated in the decision to transplant. Therefore, the primary message of our paper is that the general approach to managing this population should be centered around a principle of earlier transplantation.

Ambiguities exist surrounding whether to accept or decline an organ offer for a patient with ACLF-3, partially because data from prior investigations are conflicting regarding whether it is favorable to transplant a patient early or to wait for a higher quality liver.<sup>11</sup> However, per our results, the reduction in post-LT survival when utilizing such an organ is generally less consequential than the daily mortality while remaining on the waiting list, for all patient groups assessed. Although our prior work has suggested earlier transplantation within 30 days of listing may improve post-transplant survival,<sup>21</sup> data from the current paper indicates that within the first 7 days of listing the timing of transplantation does not impact post-LT survival. Therefore, the rationale for earlier transplantation is driven by the high waitlist mortality among candidates with ACLF-3. Subsequently, we suggest that the use of lower quality donor organs can be considered to facilitate earlier transplantation in the setting of ACLF-3, particularly in regions of the United States with higher median MELD-Na scores at LT.

An additional factor to consider when offering transplantation to candidates with ACLF-3 is whether organ failure recovery is feasible prior to LT, as this improves post-transplant survival,<sup>13,22</sup> especially among candidates above 60 years.<sup>13</sup> We therefore propose that if in the judgement of the medical and surgical providers, an opportunity exists for improvement in these specific organ system failures, then transplantation should be deferred. However, as the overall likelihood of organ failure recovery occurring within 7 days from listing is less than 10% per our study results, the general approach to the management of patients with ACLF-3 on the waiting list should be focused on early transplantation rather than postponement of LT in anticipation of future organ failure recovery. Although the relatively small percentage of patients who improved from ACLF-3 at listing to ACLF-2 at LT is notable, we believe this finding is consistent with prior data, which has demonstrated that patient's grade of ACLF between 3-7 days from hospital admission is indicative of the final ACLF grade.<sup>10</sup>

To increase confidence in the decision to proceed with LT using a high DRI organ, we have incorporated considerable variability in our 2-way sensitivity analyses, to allow the clinician to account for both the expected probability of receiving an organ offer and the estimated post-transplant survival, based on



their center's prior outcomes. However, we acknowledge that the decision to proceed with LT is complex, involving tradeoffs both at the patient and health system level. In this work, we focus only on patient-level decision making and not system-level optimization of transplant decisions. Consequently, we do not consider whether the offered organ would be better suited for another patient or would improve performance metrics for the transplantation center. The results of this work are not meant to provide a definitive recommendation on transplantation times, and clinical judgement should be the ultimate arbitrator in determining the best course for a particular patient in a given situation.

As our investigation indicates that maximum overall survival in the setting of ACLF-3 occurs with earlier LT, it is important to discuss limitations in how such patients are currently prioritized on the waiting list. Though the MELD-Na score performs well in predicting mortality for patients with mere decompensated cirrhosis, in the setting of ACLF and particularly ACLF-3, studies have demonstrated it to underestimate waitlist mortality.<sup>23–25</sup> The discrepancy between actual mortality in a patient with ACLF-3 and expected mortality as determined by the MELD-Na score is most pronounced among those with MELD-Na scores <30.<sup>11,23,24</sup> Furthermore, providing additional waitlist priority using a system based upon the MELD-Na score, such as the Share 35 rule in the United States, does not fully address the mortality risk associated with extrahepatic organ failures.<sup>25</sup> Though we do not advocate for changes in organ allocation policy based on our study findings, we do suggest additional prospective observational trials are needed to determine whether incorporation of ACLF development into waitlist prioritization leads to earlier LT and improvement in overall survival in this population.

Additionally, in the United States there is disparity across UNOS regions and between individual transplant institutions in the utilization of marginal livers, with smaller centers being more likely to decline these organs.<sup>26</sup> The reason for this discrepancy is multifactorial, but maintenance of post-transplant survival above the expected outcomes suggested by UNOS is a key driver of current clinical decision making. Subsequently, marginal quality organs are often either discarded or transplanted into patients with lower MELD-Na scores, who could afford to remain on the waiting list.<sup>26</sup> Projections have further indicated that donor organ quality will continue to worsen in the United States and if existing utilization practices remain constant, organ usage will decrease more than 30% by the year 2030.<sup>27</sup> When further considering the rising prevalence of ACLF, particularly in the population with non-alcoholic fatty liver disease,<sup>1</sup> these findings are concerning. Therefore, we suggest further investigation to explore changing the outcome metrics when utilizing a marginal quality liver for a patient with ACLF-3, so that a center is not disincentivized from performing LT in a

patient who likely would die, with an organ which may have been discarded otherwise.

Limitations that are inherent to retrospective studies of public databases also exist in our study; these were primarily related to the potential for misclassification, owing to the lack of data regarding bacterial infection or variceal bleeding, as well as the use of mechanical ventilation as a surrogate for respiratory failure. Although we cannot overcome this limitation, it should be noted that several key findings from our previous publications<sup>4,11</sup> have been subsequently corroborated in separate studies using granular patient data,<sup>24,28,29</sup> thus supporting the accuracy of our methodology to identify ACLF. Additionally, post-transplant survival, as determined in our study, may be overestimated due to a selection bias, since only the most “robust” patients in the judgement of the provider would be chosen for transplantation. This may particularly be the case for patients transplanted with marginal organs, leading to a higher relative risk of post-transplant survival compared to recipients transplanted with an optimal organ. To account for this, our 2-way sensitivity analyses provided variability in post-transplant survival, to allow the clinician to incorporate expected survival probability from their center into the decision to proceed with LT.

However, we emphasize that our results should only be used as guidance in the decision to accept an organ for transplantation, and ultimately the provider needs to also account for factors not included in our analyses such as frailty, degree of ventilatory and vasopressor requirement, and personal experience regarding transplantation with marginal quality organs.<sup>30</sup> While we cannot model all possible scenarios, given the scarcity of literature regarding transplantation in the setting of ACLF, the value of our paper is the focus on a single base case scenario and several sensitivity scenarios to provide a quantitatively driven outcome of overall survival probability in relation to 3 specific factors which have previously been demonstrated to affect pre- and post-transplant survival.<sup>11,13</sup> We believe that the sensitivity scenarios illustrate general trends useful for adapting our findings to a centers' needs.

In summary, earlier transplantation is favored for patients with ACLF-3 within the first 7 days after listing, particularly in candidates aged >60 or with 4-6 organ failures, due to a combination of high mortality without transplantation, relatively lower impact on post-transplant survival when using a marginal organ, and low likelihood of organ failure recovery prior to LT. Further research is needed regarding providing additional waitlist priority to candidates with ACLF-3 to expedite LT and remove disincentives for a center that utilizes a marginal quality donor organ in this population, to increase access to transplantation for the most critically ill patients with end-stage liver disease.

## Abbreviations

ACLF, acute-on-chronic liver failure; ACLF-3, acute-on-chronic liver failure grade 3; DRI, donor risk index; MELD, model for end-stage liver disease; UNOS, United Network for Organ Sharing.

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### Authors' contributions

Study concept and design: VS, CG, SC. Acquisition of data, analysis, and interpretation of data: VS, SPZ, SC, JP. Drafting of manuscript: VS, SPZ, CG, SC. Critical revision of manuscript for important intellectual content: VS, CD, JT, RJ, AK. Statistical analysis: VS, SPZ, SC. All authors approved the final version of the article, including the authorship list.

### Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article or its [supplementary materials](#).

### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2021.100367>.

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