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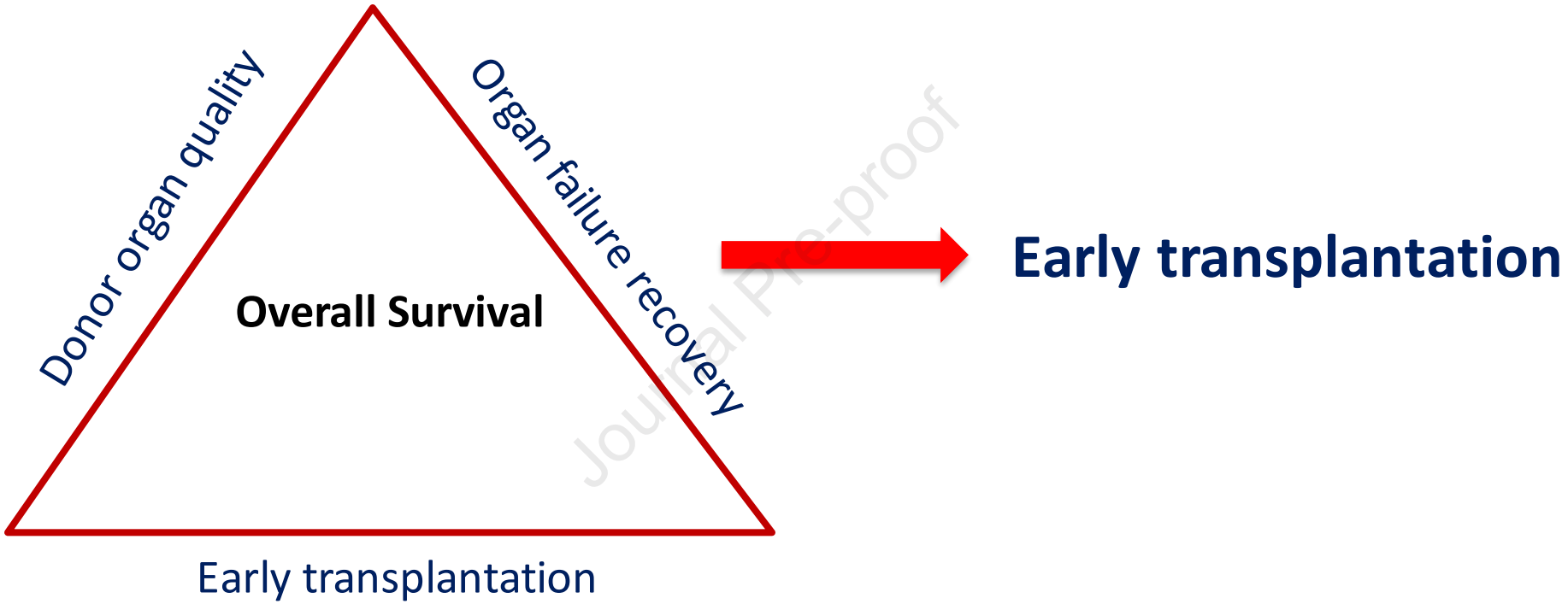

Early transplantation maximizes survival in severe acute-on-chronic liver failure: results of a Markov decision process model

Short Title: Timing of liver transplantation for severe ACLF

Suyanpeng Zhang[1], Sze-Chuan Suen PhD[1], Cynthia L. Gong PharmD PhD[2,3], Jessica Pham, BA[4], Jonel Trebicka, MD, PhD[5], Christophe Duvoux, MBBS[6], Andrew S. Klein, MD, MBA[7], Tiffany Wu, MD[8], Rajiv Jalan, MBBS, PhD[9], Vinay Sundaram MD, MSc[10]

(1) Daniel J. Epstein Department of Industrial and Systems Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, CA, USA
(2) Fetal & Neonatal Institute, Division of Neonatology, Children's Hospital Los Angeles Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
(3) Schaeffer Center for Health Policy & Economics, University of Southern California, Los Angeles, CA, USA
(4) School of Pharmacy, University of Southern California, Los Angeles, CA, USA
(5) Medical Department I, Frankfurt University Hospital, Germany; European Foundation for Study of Chronic Liver Failure, Barcelona, Spain;
(6) Medical Liver Transplant Unit-Liver Department, Henri Mondor Hospital AP-HP, Paris Est University, Créteil, France
(7) Department of Surgery and Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA
(8) Department of Medicine, Mayo Clinic, Rochester, MN, USA
(9) Liver Failure Group, Institute for Liver and Digestive Health, UCL Medical School, London, UK
(10) Karsh Division of Gastroenterology and Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA

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Acute-on-chronic liver failure (ACLF)
Acute-on-chronic liver failure grade 3 (ACLF3)
Donor risk index (DRI)
Relative risk (rr)
Donor risk index (DRI),
United Network for Organ Sharing (UNOS)

Corresponding Author Contact Information:
Vinay Sundaram, MD MsC
8900 Beverly Blvd, Suite 250
Los Angeles, CA, 09948
Phone: 310-423-6000
Fax: 310-423-0849
Email: Vinay.Sundaram@cshs.org
Orcid ID: https://orcid.org/0000-0002-1450-7756

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Rajiv Jalan is the inventor of OPA, 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.

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Abstract

Background: 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 timing of LT among patients with ACLF-3 within 7 days of listing, to maximize overall one-year survival probability.

Results: We analyzed six groups of candidates with ACLF-3: patients age ≤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 versus remaining on the waiting list for even 1 additional day ($p<0.001$), regardless of organ quality. Creation of two-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 or with 4-6 organ failures. 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 three variables.

Lay summary: In the setting of grade three 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 versus waiting 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.

Introduction

Acute-on-chronic liver failure (ACLF) is an increasingly prevalent syndrome[1] occurring in patients with decompensated cirrhosis, that is associated with severe systemic inflammation[2-4], organ failures, and high 28-day mortality[5]. The short-term mortality of certain patients with ACLF grade 3 (ACLF-3), defined as the development of three or more organ failures,[5] is particularly high [6-8] and potentially surpassing that of acute liver failure.[9] 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.[10] Liver transplantation (LT) yields excellent patient survival both at 1-year and in the long-term.[11, 12] 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 associated with reduced 1-year post-LT mortality, but also demonstrated that transplantation using an organ with a donor risk index (DRI) ≥ 1.7 predicted greater likelihood of death after LT[11]. 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.[13]

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 organ[11] and increased post-LT survival associated with organ failure recovery prior to transplantation[13].

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 consistent with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.[14]

United Network for Organ Sharing (UNOS) database analysis

From the UNOS registry (www.unos.org), we evaluated patients age 18 or older listed for liver transplantation 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 ACLF patients

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 two non-renal organ failures.[5] (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.[5] 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 liver transplant (LT) related to ACLF.[4, 9, 11] All patients analyzed had ACLF-3 at the time of listing and at transplantation. We categorized organ quality into optimal (DRI < 1.7) and marginal (DRI ≥ 1.7).[15]

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 on the next day. In our Markov decision process model, we accounted for the following factors: patient age > or ≤ 60 years[13], 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 α, and the likelihood of receiving a marginal organ as 1-α. Because the probability of receiving an organ offer varies across UNOS regions, we examined different values of α. For instance, if a center has an expected 70% probability of a liver offer, then α would be 0.7. (Figure 1) We utilized two Markov processes: the pre-transplant process (Figure 1, top box) and the post-transplant process (Figure 1, bottom box). On each day t after listing, the candidate has a non-transplant mortality probability of γ_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[16, 17] designed to maximize expected one-year survival, given all possible decisions on each day (supplemental appendix, section 1). Length of hospital stay do not differ substantially between patients with earlier or later transplants, and we therefore omit this consideration from our analysis. The difference in post-LT survival probability when transplanted with a marginal versus optimal organ was estimated by

the relative risk (rr). (Figure S1) In our base case analysis, we used 0.9 as the relative risk, but we varied the rr from 0.6 to 0.9 in sensitivity analyses.

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 (α) and the relative risk of survival for a marginal organ (rr) in two-way graphs. Exact equations and details for both can be found in the supplemental document.

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 variable. Survival 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 ≤ 60 years or the presence of 3 or 4-6 organ failures at waitlist registration. We did create additional stratifications within these subgroups, such as patients above 60 years of age 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 failure and1,816 (31.1%) patients with 4-6 organ failures. Mean 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 Figure S2**Error! Reference source not found.**. By the seventh day, the survival probability is 60.3% for ≤60 aged patients and 52.8% for patients above 60 years (p=0.009). When examining of 3 versus 4-6 organ failures, we found that by day 7, the survival probability was 62.7% for

patients with three 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 Figure S3. In Figure S3a, survival after LT is depicted according to age and donor organ quality. Among patients younger than 60 years the one-year survival probability is 86.2% when transplanted with low DRI liver and 78.2% using a high DRI organ. Among recipients > 60 years old, one-year survival after LT was 77.1% using an optimal liver and 74.1% with a marginal liver. Figure S3b shows similar post-LT survival, categorized by number of organ failures at listing and the type of donor organ. When transplanted with an optimal liver, the one-year survival probability is 86.5% for a patient with 3 organ failures versus 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 four patient subgroups (figures 2a-2d), 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 figure 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 (figure 2b), with a 5.2%

difference in overall survival from day 1-7 after listing (p<0.001). In figures 2c and 2d, survival probabilities are displayed among patients categorized according to age. For candidates ≤ 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 one 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 one-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% (α = 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 one-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 one-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. Figures 3a-3d display two-way sensitivity analyses depicting the maximum number of days to wait for an optimal liver, based on expected probability of receiving an offer and 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 one-year survival when transplanted with a marginal 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 figure 3a, we display a scenario of a transplant candidate > 60 years old. In this setting, if the center has an expected one-year survival of 70% for patients transplanted with a marginal liver and 50% daily likelihood of being offered an optimal liver, then LT should proceed on day 1 if an organ is offered, regardless of quality. (Figure 3a, red star) However, if the patient is ≤ 60 years old, the center can wait until day 2 before accepting a marginal organ. (Figure 3b, red star). We describe additional scenarios according to the presence of 3 or 4-6 organ failures at waitlist registration in figures 3c and 3d.As expected, the decision boundaries occur earlier for patients above

age 60 or with 4-6 organ failures at listing, indicating survival benefit with shorter waiting time.

Hepatic versus 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 two-fold. 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.[13] Survival probabilities are summarized in table S4. Figure S7 depicts the effect of variation in the relative risk and probability of optimal organ offer. For instance, if the center has an expected one-year survival of 70% for patients transplanted with a marginal liver and 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 (Figure S7a, red star). However, if the patient has extrahepatic ACLF-3, the center can wait until day 2 before accepting a marginal organ (Figure 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.[13] (Figure S4) We restructured the model by introducing two 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 the strategy determined by our model.

Sensitivity analyses

We performed two 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.[18] After removal of 582 patients with suspected CKD (9.9%), we demonstrated similar decision boundaries across all four patient groups. (Figure 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.[19] 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. (Figure 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 four patient groups studies, the day of transplantation did not significantly affect length of hospital stay after LT. (table S5)

Discussion

Our study demonstrates that among the three 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 above age 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 found in prior prospective studies[10, 20], 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 ALCF-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.[11] 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 [21], 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 substantially 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,[13, 22] especially among candidates above 60 years.[13] 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 findings 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.[10]

To increase confidence in the decision to proceed with LT using a high DRI organ, we have incorporated considerable variability in our two-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 both 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 ACLF and particularly ACLF-3, studies have demonstrated it to underestimate waitlist mortality.[23-25] The discrepancy between the actual mortality in a patient with ACLF-3 and the expected mortality as determined by the MELD-Na score is most pronounced among those with MELD-Na scores < 30.[11, 23, 24] 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 extra-hepatic organ failures.[25] 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 particularly higher rates of declining these organs in smaller centers.[26] 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.[26] 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.[27] When further considering the rising prevalence of ACLF, particularly in the NAFLD population[1], these findings are concerning. Therefore, we suggest further investigation to explore changing the outcomes metrics when utilizing a marginal quality liver into a patient with ACLF-3, so that a center is not disincentivized for performing LT in a patient who likely would die, with an organ which may have been otherwise discarded.

Limitations that are inherent in retrospective studies of public databases also exist in our study, however, primarily related to the potential for misclassification, concerning the lack of data regarding bacterial infection or variceal bleeding, as well as using mechanical ventilation as an indicator for respiratory failure. Although we cannot overcome this limitation, it should be noted that several key findings from our previously publications[4, 11] have been subsequently corroborated in separate studies using granular patient data,[24, 28, 29] thus supporting the accuracy of our methodology to identify ACLF. Additiionally, 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 two-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 be used only 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.[30] While we cannot model all possible scenarios, given the sparsity 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 three specific factors which have been previously demonstrated to affect pre and post-transplant survival.[11, 13] 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 above age 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 removing 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.

References

[1] Sundaram V, Jalan R, Shah P, Singal AK, Patel AA, Wu T, et al. Acute on chronic liver failure from nonalcoholic fatty liver disease: a growing and aging cohort with rising mortality. Hepatology 2020.
[2] Claria J, Arroyo V, Moreau R. The Acute-on-Chronic Liver Failure Syndrome, or When the Innate Immune System Goes Astray. Journal of immunology 2016;197:3755-3761.
[3] Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. Hepatology 2016;64:1249-1264.
[4] Sundaram V, Jalan R, Ahn JC, Charlton MR, Goldberg DS, Karvellas CJ, et al. Class III obesity is a risk factor for the development of acute-on-chronic liver failure in patients with decompensated cirrhosis. Journal of hepatology 2018;69:617-625.
[5] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426-1437, 1437 e1421-1429.
[6] Arroyo V, Moreau R, Jalan R, Gines P, Study E-CCC. Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis. Journal of hepatology 2015;62:S131-143.
[7] Arroyo V, Moreau R, Kamath PS, Jalan R, Gines P, Nevens F, et al. Acute-on-chronic liver failure in cirrhosis. Nature reviews Disease primers 2016;2:16041.
[8] Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Gines P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. Journal of hepatology 2014;61:1038-1047.
[9] Sundaram V, Shah P, Wong RJ, Karvellas CJ, Fortune BE, Mahmud N, et al. Patients With Acute on Chronic Liver Failure Grade 3 Have Greater 14-Day Waitlist Mortality Than Status-1a Patients. Hepatology 2019.
[10] Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62:243-252.
[11] Sundaram V, Jalan R, Wu T, Volk ML, Asrani SK, Klein AS, et al. Factors Associated with Survival of Patients With Severe Acute on Chronic Liver Failure Before and After Liver Transplantation. Gastroenterology 2018.
[12] Sundaram V, Mahmud N, Perricone G, Katarey D, Wong RJ, Karvellas CJ, et al. Long-term outcomes of patients undergoing liver transplantation for acute-on-chronic liver failure. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2020.
[13] Sundaram V, Kogachi S, Wong RJ, Karvellas CJ, Fortune BE, Mahmud N, et al. Effect of the clinical course of acute on chronic liver failure prior to liver transplantation on post-transplant survival. Journal of hepatology 2019.
[14] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bmj 2007;335:806-808.
[15] Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2006;6:783-790.
[16] Bellman R. Functional Equations in the Theory of Dynamic Programming: Viii. The Variation of Green's Functions for the One-Dimensional Case. Proc Natl Acad Sci U S A 1957;43:839-841.
[17] Bellman R, Kalaba R. Dynamic Programming and Statistical Communication Theory. Proc Natl Acad Sci U S A 1957;43:749-751.

[18] Cullaro G, Verna EC, Lee BP, Lai JC. Chronic Kidney Disease in Liver Transplant Candidates: A Rising Burden Impacting Post-Liver Transplant Outcomes. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2020;26:498-506.
[19] Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148:547-555.
[20] Trebicka J, Fernandez J, Papp M, Caraceni P, Laleman W, Gambino C, et al. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. Journal of hepatology 2020;73:842-854.
[21] Sundaram V, Jalan R. Reply. Gastroenterology 2019;157:1163-1164.
[22] Huebener P, Sterneck MR, Bangert K, Drolz A, Lohse AW, Kluge S, et al. Stabilisation of acute-on-chronic liver failure patients before liver transplantation predicts post-transplant survival. Alimentary pharmacology & therapeutics 2018;47:1502-1510.
[23] Abdallah MA, Kuo YF, Asrani S, Wong RJ, Ahmed A, Kwo P, et al. Validating a novel score based on interaction between ACLF grade and MELD score to predict waitlist mortality. Journal of hepatology 2020.
[24] Hernaez R, Liu Y, Kramer JR, Rana A, El-Serag HB, Kanwal F. Model for end-stage liver disease-sodium underestimates 90-day mortality risk in patients with acute-on-chronic liver failure. Journal of hepatology 2020.
[25] Sundaram V, Shah P, Mahmud N, Lindenmeyer CC, Klein AS, Wong RJ, et al. Patients with severe acute-on-chronic liver failure are disadvantaged by model for end-stage liver disease-based organ allocation policy. Alimentary pharmacology & therapeutics 2020.
[26] Volk ML, Reichert HA, Lok AS, Hayward RA. Variation in organ quality between liver transplant centers. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2011;11:958-964.
[27] Orman ES, Mayorga ME, Wheeler SB, Townsley RM, Toro-Diaz HH, Hayashi PH, et al. Declining liver graft quality threatens the future of liver transplantation in the United States. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 2015;21:1040-1050.
[28] Artzner T, Michard B, Weiss E, Barbier L, Noorah Z, Merle JC, et al. Liver transplantation for critically ill cirrhotic patients: Stratifying utility based on pretransplant factors. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2020.
[29] Mahmud N, Kaplan DE, Taddei TH, Goldberg DS. Incidence and Mortality of Acute on Chronic Liver Failure using Two Definitions in Patients with Compensated Cirrhosis. Hepatology 2019.
[30] Weiss E, Giabicani M, Saner F. Do Liver Transplantation Criteria Differ According to the Type of Donor and the Severity of the Recipient? Transplantation 2021;105:e32.

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

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	Source
ACLF3 patients non-transplant survival probabilities (1-$\gamma_{\square}$), by age and day (1-7):		UNOS
>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	
ACLF3 patients post-transplant survival probabilities (1-μ_{12}) transplanted in the first week:		UNOS
Optimal Liver		
>60 yo, 12 mo post-transplant	0.7709	
≤60 yo, 12 mo post-transplant	0.8618	
Marginal Liver		
>60 yo, 12 mo post-transplant	0.7407	
≤60 yo, 12 mo post-transplant	0.7819	
ACLF3 patients non-transplant survival probabilities (1-γ_t), by organ failures and day (1-7):		UNOS
>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	
ACLF3 patients post-transplant survival probabilities (1-μ_{12}) transplanted in the first week:		UNOS
Optimal Liver		
>3 of, 12 mo post-transplant	0.7922	
=3 of, 12 mo post-transplant	0.8654	
Marginal Liver		
>3 of, 12 mo post-transplant	0.6963	
=3 of, 12 mo post-transplant	0.8030	
Relative risk of post-transplant mortality between transplantees with a marginal versus an optimal liver (rr)	0.90 (varied in sensitivity analysis)	
Daily probability of getting an optimal liver (α)	0.6 (varied in sensitivity analysis)	

Figure 1: Diagram of patient flow while awaiting liver transplantation

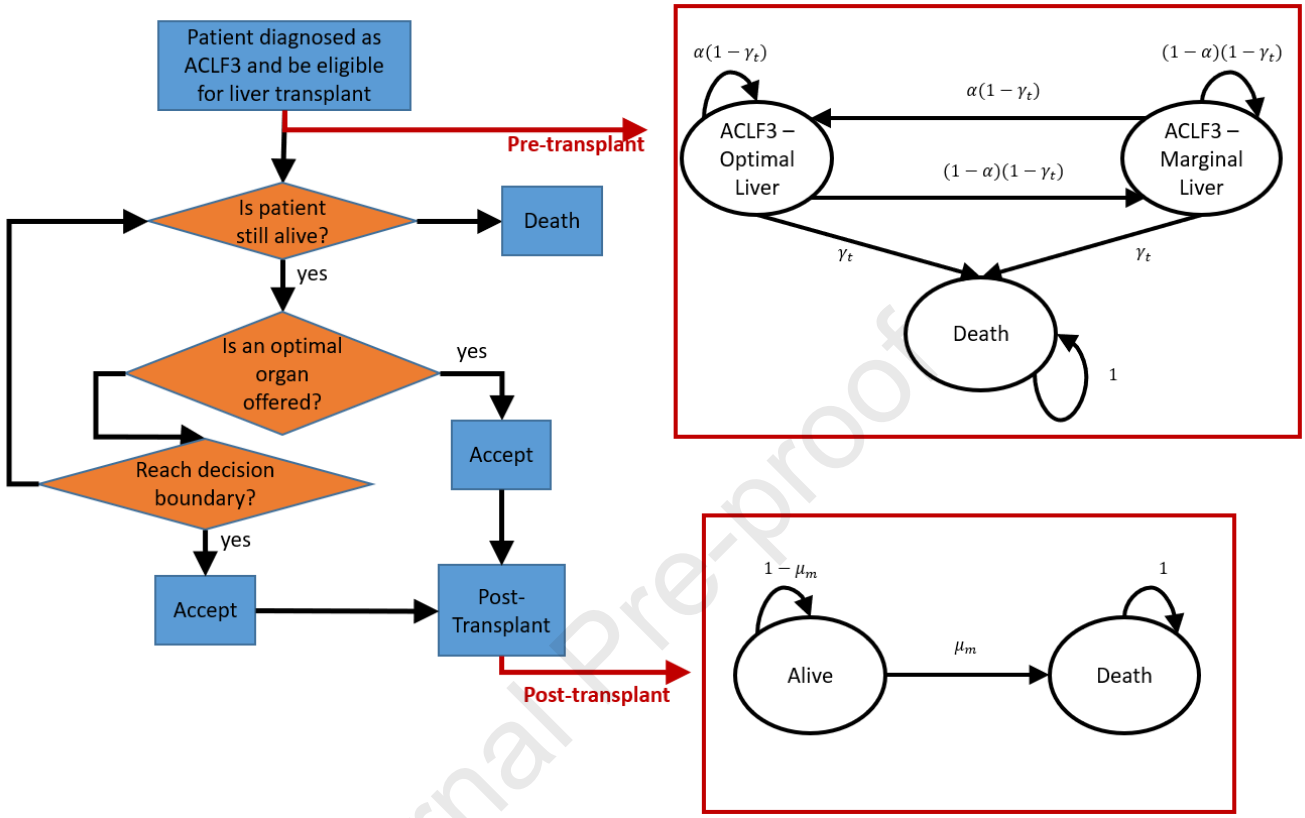


Figure 2. Overall 1-year survival probability based on the decision to transplant on a specific day or defer LT for one day

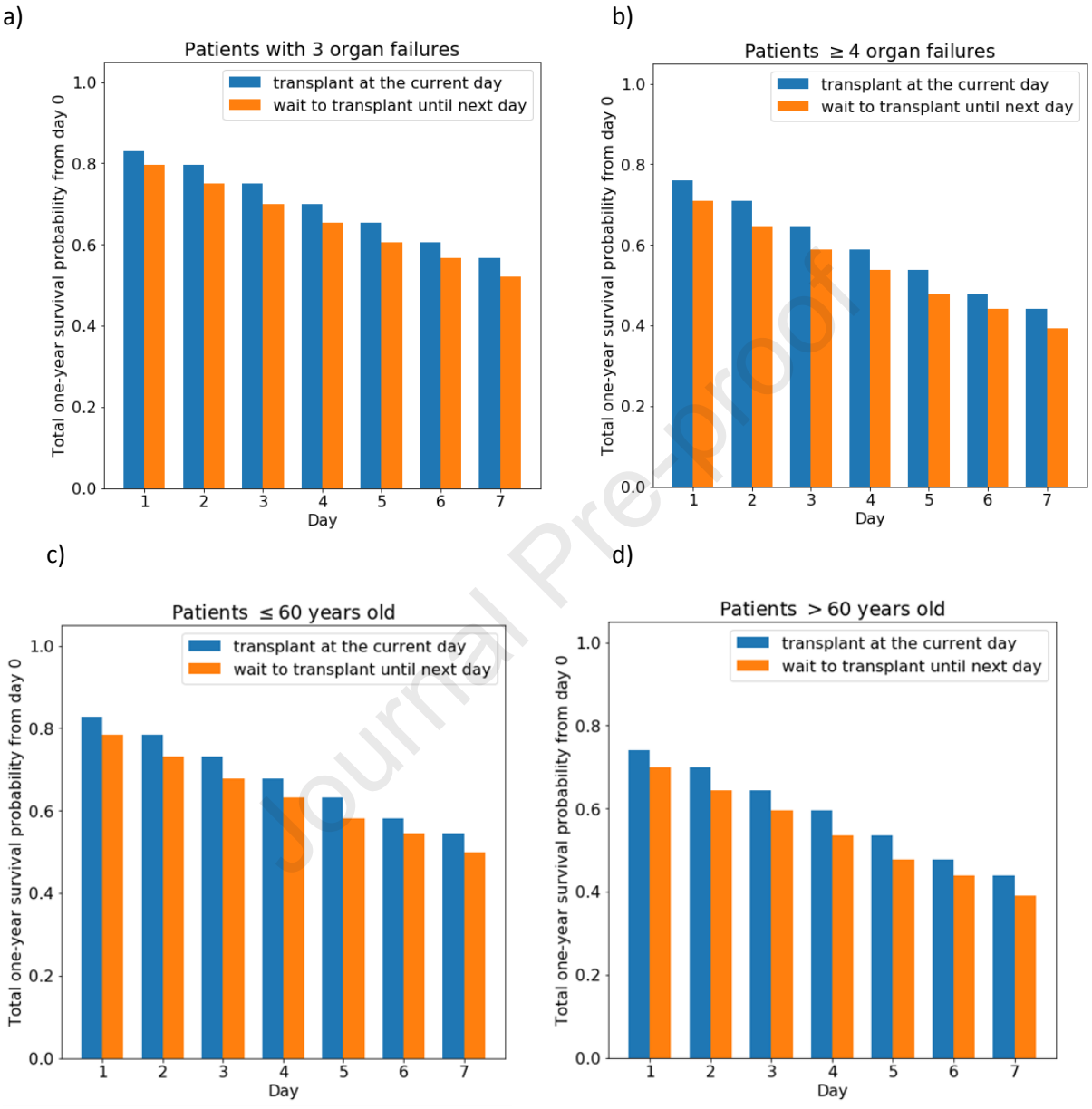
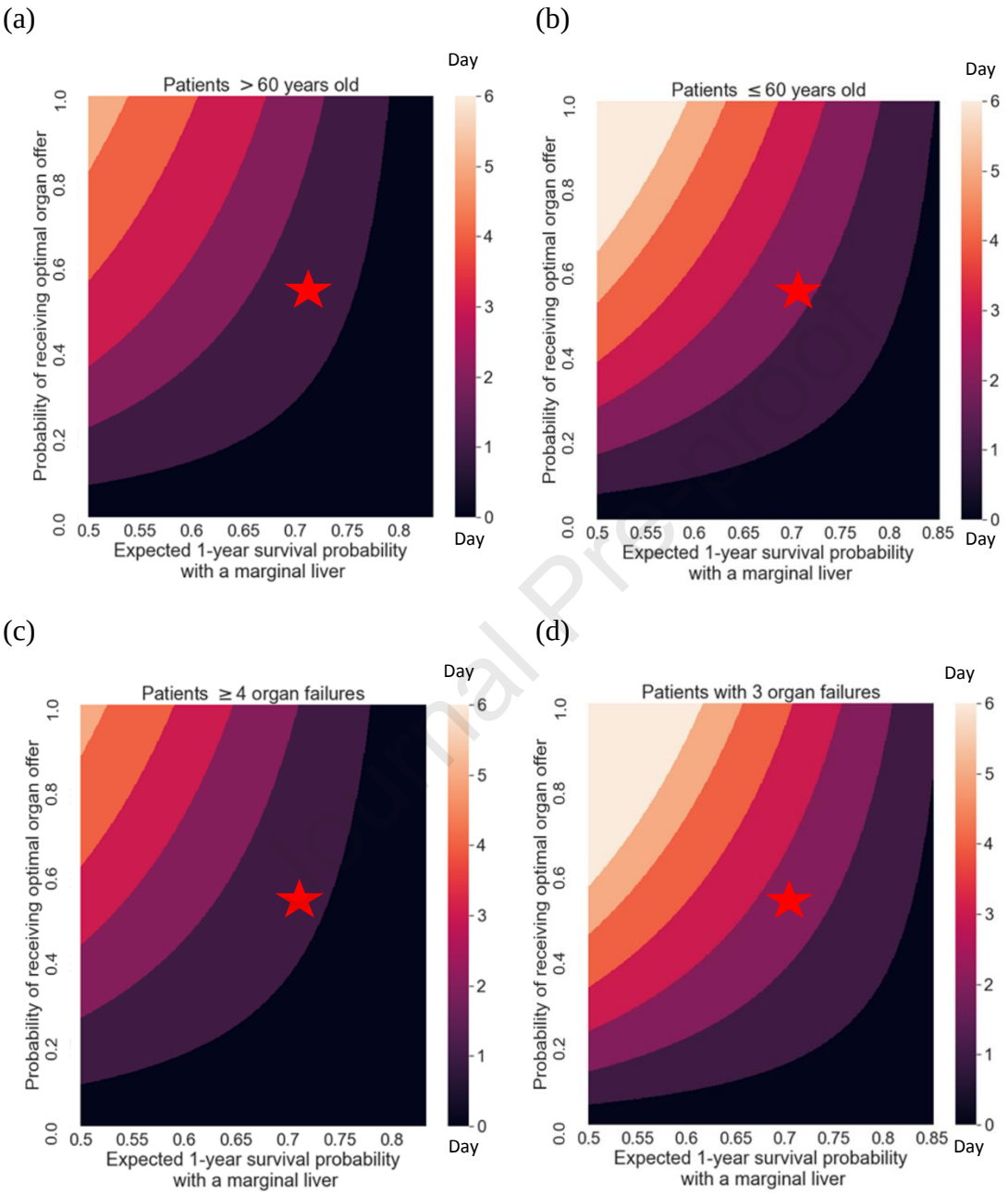


Figure 3. Two-way sensitivity analyses, accounting for center variation regarding probability of receiving an optimal organ offer and expected 1-year post-LT survival using a marginal quality organ



Legend: In figure 3a, 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 to maximize overall survival. (Figure 3a, red star) However, if the patient is ≤ 60 years old, then LT can occur on day 2 before regardless of organ quality. (Figure 3b, red star). Additional scenarios according to the presence of 3 or 4-6 organ failures at waitlist registration are depicted in figures 3c and 3d.

Highlights

- We created a Markov decision process model to maximize overall survival among patients listed for liver transplantation with grade three acute-on-chronic liver failure (ACLF-3) within the first 7 days of listing
- We analyzed three independent factors associated with overall survival in this setting: a) proceeding with earlier transplantation b) delaying transplantation until receiving an offer of an optimal donor organ based on a donor risk index of < 1.7 c) delaying transplantation until organ failure recovery and improvement from ACLF-3 to ACLF-2
- Among these three factors, earlier transplantation maximizes overall survival probability. This is driven by the high waitlist mortality of patients with ACLF-3
- Although transplantation with a marginal organ does reduce post-transplant survival, the relative impact is generally less consequential as compared to the high mortality of delaying transplantation
- The likelihood of organ failure recovery was found to be less than 10%, indicating that transplantation should not be deferred for this purpose