Outcomes in the 2018 UNOS donor heart allocation system: A perspective on disparate analyses

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Abstract

The United Network for Organ Sharing (UNOS) implemented a revised donor heart allocation system on October 18, 2018 with principle aims to reduce waitlist mortality, enhance geographic organ sharing, and improve organ distribution equity. Five recently published analyses compared outcomes of heart transplant (HT) recipients transplanted under the revised versus previous system. All demonstrated increased pre-transplant temporary mechanical circulatory support use and graft ischemic times under the revised system. However, despite using data from the same UNOS Registry, three analyses demonstrated increased risk of post-transplant mortality under the revised system, while two others found no significant difference in mortality risk. These studies differed in their analytic cohorts, study periods, follow-up duration, and statistical methodologies. Additionally, some may have introduced survivor bias or violated non-informative censoring. Given these variable findings, longer-term outcome assessment is warranted before the HT community can truly understand the impact of the 2018 UNOS system revision on post-transplant outcomes.

Keywords

heart transplantation; mechanical circulatory support; post-transplant outcomes; United Network of Organ Sharing; donor heart allocation system; UNOS Registry

> "You can't always get what you want…But if you try sometimes, well, you might find you get what you need"
>
> Sir Michael Philip (Mick) Jagger, English singer, song-writer (1943–)

The United Network for Organ Sharing (UNOS) implemented a revised donor heart allocation system on October 18, 2018 with the principal aims of reducing waitlist mortality, enhancing geographic organ sharing, and improving organ distribution equity.[1]

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Since then, 5 reports comparing the outcomes of heart transplant (HT) recipients under the revised system with those transplanted within the previous system have emerged (Table 1).[2–6] All studies demonstrated increased utilization of pre-transplant temporary mechanical circulatory support (MCS) and longer graft ischemic times under the revised system. Furthermore, most analyses found that the revised system was associated with decreased waitlist mortality but longer travel distance between donor and recipient centers. However, despite using similar data from the same UNOS Registry, there were discrepant findings in the association between the adoption of the revised system and post-transplant outcomes. A total of 3 reports found an increased risk of post-transplant mortality under the revised system,[2,4,6] whereas the other 2 found no statistically significant difference.[3,5] Understanding what accounts for these disparities is important to delineate for the HT community to improve patient care under the revised allocation system. In addition, outlining methodologic differences between the analyses of the same dataset provides an opportunity to highlight key considerations for future investigative efforts, as has been done previously in the field of advanced heart disease.[7]

Cogswell et al[2] compared 6,001 adult patients who were listed and transplanted in the prior system with 539 patients in the revised system between October 2015 and March 2019. The aforementioned study demonstrated an increased risk of post-transplantation mortality or retransplantation in the revised system at 6 months follow-up (adjusted hazard ratio [aHR]: 2.1, 95% CI: 1.4–2.9). In addition, this analysis found lower waitlist mortality, higher pre-transplant use of temporary MCS, and lower rates of pre-transplant durable left ventricular assist device use during the revised system period. Using similar analytical methods on the same dataset with a larger cohort of HT recipients during the revised system period (prior system, N = 2,371; revised system, N = 1,311), Kilic et al[4] demonstrated similar findings with an aHR of 1.41 (95% CI: 1.01–1.95) for post-transplant mortality under the revised system. Trivedi et al[6] also found higher rates of post-transplant mortality at 6 months for HT recipients under the revised system (23% vs 7%, $p < 0.01$).

Jawitz et al[3] closely mirrored the analytical design of Cogswell et al.[2] Notably, this analysis included more patients (prior system, N = 6,004; revised system, N = 1,115), had a longer follow-up to September 2019, and found an 18% increase in the hazard of post-transplant mortality or retransplantation under the new allocation system. However, this increase did not reach a statistical significance (log rank $p = 0.075$), and the CIs were wide (95% CI: 0.90–1.55). Although this study did not report the survival outcomes of waitlisted patients, it did demonstrate longer graft ischemic times and increased temporary MCS utilization in the revised system, similar to other studies. Consistent with the findings of Jawitz et al,[3] Goff et al[5] found no statistically significant difference in post-transplant survival rates in an unadjusted analysis (92.8% vs 93.6%), and further showed that waitlist mortality was not different between the 2 periods when patients were followed until November 2019.

There are several factors that could explain the disparate findings between these analyses despite use of the same UNOS dataset. First, the studies differed in their analytical cohorts. For instance, Jawitz et al[3] included roughly twice the number of patients in the revised group compared with Cogswell et al[2] and Trivedi et al.[6] Goff et al[5] also included more patients in the revised group but did not exclude recipients who were listed before but

were transplanted after the implementation of the revised policy on October 18, 2018, as was done by Jawitz et al[3] and Cogswell et al.[2] This may have introduced the immortal time/survivor bias because these patients had to survive until the end of the prior system in order to be transplanted during the revised system. Because patients listed and transplanted under the revised system appear to have greater illness severity, including those patients listed in the prior system but transplanted in the revised system may have also diminished illness severity and improved post-transplant outcomes of the revised system patient cohort. Furthermore, not accounting for this delay period could have resulted in either a spurious survival advantage or disadvantage in the revised system. The studies also differed in the temporal definition of the prior system. Cogswell et al[2] and Jawitz et al[3] included patients from October 18, 2015 onward, Trivedi et al[6] included patients from January 1, 2016 onward, Goff et al[5] included patients from October 18, 2017 onward, and Kilic et al[4] included patients from January 1, 2018 onward. These differences may have influenced the survival rates in the prior system groups for each study.

A second explanation relates to the possible violation of the non-informative censoring assumption. In the context of survival analyses, censoring ought to be non-informative such that participants who are censored from a study should be censored for reasons unrelated to the study.[8] In the case of the revised UNOS donor heart allocation system, the survival time and censor time may not be independent. Thus, it is possible that censored patients may have a higher survival rate when there are heavily censored data, a finding that was previously pointed out in response to the Cogswell et al analysis.[9] Along these lines, varying follow-up times among these studies could have inherently contributed to survival differences. For instance, Jawitz et al[3] and Goff et al[5] included an additional 3 and 4 months of data, respectively, compared with Cogswell et al[2] and Kilic et al.[4] Shorter follow-up times in the setting of existing discrepancies in UNOS data submission requirements may introduce ascertainment bias where all events are accounted for, but surviving patients are more likely to be censored. This aspect was evident in the Cogswell et al[2] study, which had 45 patients remaining at risk at 100 days, vs over 800 and 428 patients remaining at risk at the same time in the Goff et al[5] and Jawitz et al[3] reports, respectively. Indeed, when such biases were accounted for with more contemporary follow-up data in response to the Cogswell et al[2] report, the harm signal associated with the revised system was no longer statistically significant.[10] Moreover, given that this policy change resulted in rapid shifts in care patterns, these data should be reanalyzed in a manner that takes into account time-dependent changes in clinical decision making. Specifically, examining pre-transplant care patterns and post-transplant outcomes soon after the revised system was implemented (e.g., within 3 months) and comparing with later time periods (e.g., 6-month intervals) may uncover important changes in clinical practice and/or patient outcomes. This was the case in France, where bridging to HT with venoarterial extracorporeal membrane oxygenation was initially associated with decreased post-transplant survival.[11] However, with the adoption of a protocol detailing patient selection, implant strategy, and peri-operative management, such patients were later found to have acceptable outcomes.[12] A final factor that may have contributed to differing top-line results is that all the studies except for Goff et al[5] and Trivedi et al[6] performed risk adjustment using multivariable regression analysis, which can be prone to biases owing to differences in model building and covariate selection. For

example, the inclusion of pre-transplant extracorporeal membrane oxygenation or temporary MCS use and donor graft ischemic times as covariates likely influenced aHR estimates, as these have clearly changed in the revised system era and are known to be associated with post-transplant outcomes. However, it is unclear whether these factors are mediators of post-transplant outcomes or confounders; they are likely both. Thus, it would be informative for future analyses to report the unadjusted hazard ratios and aHRs that do and do not account for such covariates.

So, where do we go from here? Although it is difficult to quantify the individual effects of the above factors, they must be taken into account while interpreting the findings from this series of studies, and methodologic transparency of future investigations should be encouraged. In addition, because the 95% CIs in the 3 analyses that reported aHRs were quite wide, it is clear that the assessment of longer-term post-transplant outcomes is warranted before the HT community will be able to truly understand the potential benefits and harms of the revised UNOS donor heart allocation system. Given the unanticipated, substantial increase in exception requests since the 2018 policy revision,[13] future analyses should also stratify HT recipients by exception status. Such knowledge may inform modifications of the allocation policy in the future or assist in the development of a heart allocation score.

Notably, all the studies found increased rates of temporary MCS use before HT and longer graft ischemic times after the system revision. These results highlight several important aspects. First, the clinical profile of allograft recipients has shifted in the contemporary era, and this may be commensurate with shifting physician- and hospital-level practices.[14] Expected post-transplant survival estimates should account for this sicker pre-transplant patient phenotype. Such a strategy could reveal that despite higher expected mortality, the observed mortality in the revised system era is preserved (or possibly improved). However, this approach would require a periodic updating of predicted mortality risk to establish a new normal as the HT community gains additional experience in this construct and patient outcomes evolve. Second, thoughtful investigations to further define appropriate patient selection for transplant listing as well as optimal bridging approaches to HT with or without MCS are needed. Third, these studies call to action the need for strategies to decrease donor graft ischemic times or to more adequately support donor grafts *ex vivo*. Indeed, the results of ongoing studies of novel technology for warm, beating heart transport are eagerly awaited. Finally, the HT community should be committed to critical review of these and future investigations and be open to re-revising the donor heart allocation policy to ensure that unintended consequences are addressed, and patient outcomes are not compromised.

As in the case of the 2018 UNOS system revision, future regulatory changes will undoubtedly have significant intended and unintended consequences on transplant centers and patients. Although a rigorous evaluation of the impact of such changes on post-transplant survival will always be important, it will also be useful to develop metrics of expected changes in care processes, post-transplant mortality, and other outcomes such as risk of primary graft dysfunction before a widespread policy implementation. These measures could be developed by modeling anticipated changes in care patterns (e.g., increased temporary MCS utilization). Then, using historical data from the UNOS Registry,

estimated associations between such clinical changes and post-transplant outcomes could be derived *a priori*. This approach could enable the creation of benchmark rates of key patient outcomes, and the associations between future policy changes and subsequent observed patient outcomes could then be compared with expected values. Moreover, recognizing that post-transplant outcomes are influenced by other concomitant changes such as expanding donor pools (including patients with hepatitis C virus or opioid overdose) and advancements in durable and temporary MCS technologies, is important to take into consideration. Ultimately, such strategies would help contextualize observed changes in patient outcomes after major policy changes, identify key areas for future investigation, and allow the HT community to continue its laser focus on improving outcomes of donor heart recipients.

Disclosure statement

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Table 1

Comparisons of Patient Characteristics, Methodologies, and Results of 5 Contemporary Evaluations of Post-Transplant Outcomes in the Revised UNOS Donor Heart Allocation System

Study	Cogswell et al[2] JHLT 2020	Kilic et al[4] Circulation 2020	Jawitz et al[3] JACC Heart Failure 2020	Goff et al[5] AJT 2020	Trivedi et al[6] ASAI0 J 2020
Cohort	Waitlisted and transplanted: prior system—6,001 revised system—539	Waitlisted: prior system—3,258 revised system—1,759 Transplanted: prior system—2,371 revised system—1,311	Waitlisted and transplanted: prior system—6,004 revised system—1,115	Waitlisted: prior system—7,418 revised system—5,790 Transplanted: prior system—2,954 revised system—3,302	Waitlisted: prior system—10,824 revised system—1,544 Transplanted: prior system—6,739 revised system—664
Study period	October 18, 2015–March 31, 2019	January 1, 2018–March 31, 2019	October 17, 2015–June 30, 2019	October 18, 2017–May 17, 2019	January 1, 2016–March 31, 2019
Exclusion of recipients listed before but transplanted after October 15, 2018	Yes	Unclear	Yes (n = 671 patients)	No	No
End follow-up time	June 2019	June 2019	September 2019	November 2019	September 2019
Primary outcome of interest	Mortality or retransplantation	Mortality	Mortality or retransplantation	Mortality	Mortality
Statistical methods	Time-to-event Kaplan–Meier analysis MuInvariable Cox regression analysis 1:1 propensity matching for sensitivity analysis Competing risks regression for waitlist outcomes	Time-to-event Kaplan–Meier analysis Multivariable Cox regression analysis Competing risks regression for waitlist outcomes	Time-to-event Kaplan–Meier analysis Multivariable Cox regression analysis 1:1 propensity matching for sensitivity analysis	Time-to-event Kaplan–Meier analysis	Time-to-event Kaplan–Meier analysis
Revised system vs prior system for post-transplant survival	↓ Unadjusted post-transplant survival at 6 months (77.9% vs 93.4%) ↑ Adjusted risk of post-transplant mortality (aHR 2.1 [95% CI: 1.4–2.9])	↓ Unadjusted post-transplant survival at 6 months (86.5% vs 93.7%) ↑ Adjusted risk of post-transplant mortality (aHR: 1.41 [95% CI: 1.01–1.95])	↓ Unadjusted post-transplant survival at 6 months (90.6 vs 93.3%) No difference in adjusted risk of post-transplant mortality (aHR: 1.18 [95% CI: 0.90–1.55]) Findings persisted after propensity-score matching	No difference in unadjusted post-transplant survival at 6 months (92.8% vs 93.6%)	↓ Unadjusted post-transplant survival at 6 months (77% vs 93%)
Waitlist outcomes after policy revision	↓ Mortality	↓ Mortality	Not reported	No change in mortality	Not reported
Findings that are common after policy revision	↑ Temporary MCS bridging, ↓ durable LVAD bridging, ↑ recipient graft ischemic times				

Abbreviations: aHR, adjusted hazard ratio; AJT, American Journal of Transplantation; ASAIO J, American Society for Artificial Internal Organs Journal; JACC, Journal of the American College of Cardiology; JHLT, Journal of Heart and Lung Transplantation; LVAD, left ventricular assist devices; MCS, mechanical circulatory support.