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# Call for Changes in Lung Allocation to Reduce Transplant Wait-List Mortality for Cystic Fibrosis

As lung transplantation is becoming increasingly common, the challenges involved in optimizing organ allocation and minimizing wait-list mortality are escalating. The demand for donor organs exceeds supply, making it imperative to allocate organs to individuals with the greatest need to maximize benefit from a scarce resource. The "common rule" mandate from the Department of Health and Human Services in 1999 requires that donor organs be allocated to the sickest patients first. To address this challenge, allocation based on wait-list time was replaced by the Lung Allocation Score (LAS) in 2005, which was used to distribute donor lungs based on parameters that predicted wait-list mortality, balanced twofold relative to factors that predicted 1-year survival (1). Since its implementation, the LAS has undergone revisions as additional data have provided clinical parameters predictive of wait-list mortality and/or 1-year post-transplant survival, and overall wait-list mortality has improved (2). Moreover, a lawsuit in 2017 led to the removal of some geographic constraints to organ allocation and prompted an evaluation of geographic sharing that has the potential to reduce wait-list mortality (3, 4). Despite these efforts, however, the LAS remains limited in its ability to identify patients who are most likely to benefit from transplantation. The wait-list mortality for patients with cystic fibrosis (CF) clearly illustrates this problem.

A major challenge for individuals with CF is that survival with advanced disease is heterogeneous. Although the median survival with $FEV_1 < 30\%$ predicted is 6.6 years, annual mortality is ~10% without transplantation (5). Although short-term survival may improve with the development of effective CFTR (CF transmembrane conductance regulator) modulators, the high risk of death in advanced CF lung disease prompted a strong recommendation for early transplant referral to provide a survival option for individuals who suffer a precipitous decline resulting in respiratory failure (6). Problematically, the wait-list mortality for individuals with CF has remained at >10% since implementation of the LAS (7). Experienced CF healthcare providers consider this wait-list mortality unacceptable because individuals with CF typically enjoy more dramatic quality-of-life improvements and a median post-transplant survival approaching 10 years, which is longer than that observed in individuals with other lung diseases (8, 9). Why is the wait-list mortality so high? One potential explanation is that the LAS does not consider many CF-specific patient characteristics associated with short-term mortality. Modification of the LAS by using CF-specific risk factors might improve the ability of the LAS to prioritize access to transplantation for patients with CF and the highest risk of wait-list mortality.

In a study presented in this issue of the *Journal*, Lehr and colleagues (pp. 1013–1021) addressed this problem by merging two datasets: the Scientific Registry of Transplant Recipients, which contains information on wait-list mortality and post-transplant survival, and the CF Foundation Patient Registry (CFFPR), which includes unique longitudinal data on more than 28,000 individuals with CF (10). The datasets were merged rigorously and provided a large sample. Using the combined dataset, the authors first updated the current LAS model (updated LAS revised [LAS-RU]) based on patients who were listed and/or underwent transplantation between 2011 and 2014. The authors then evaluated how variables from the CFFPR impacted the LAS-RU and derived a new LAS, termed LAS-RU-CF. Their analysis identified that for patients with CF, the trajectory of $FEV_1$ decline, colonization with any *Burkholderia* species, hospitalization days, and massive hemoptysis were associated with wait-list mortality, and pulmonary exacerbation time was associated with post-transplant mortality. Most importantly, inclusion of the variables from the CFFPR increased variability in the LAS score and LAS rank for patients with CF, and thus improved the predictive accuracy of the modified LAS (LAS-RU-CF). In aggregate, the modified LAS would potentially prioritize organ allocation to individuals with CF who would be most likely to benefit from transplantation. In addition, the combined database exemplifies the potential for detailed, longitudinal, disease-specific databases to facilitate mortality



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risk prediction. To inform further LAS revisions, additional databases for other transplant indications are sorely needed.

Are Lehr and colleagues justified in stating that the LAS-RU-CF has superior predictive accuracy compared with prior models? Although the LAS score and rank changed for patients with CF, the overall model performance did not improve. This result is counterintuitive, and it may reflect the fact that individuals with CF accounted for only a small minority of transplant registrants in the study cohort (~10%). We suspect that a model including only CF would show that the LAS-RU-CF has improved predictive accuracy. If so, this scenario would illustrate a bigger problem in risk prediction. Lung transplantation is an intervention for heterogeneous populations, but the LAS is insensitive to population-specific factors. Instead of one combined predictive model, perhaps there should be disease-specific models incorporating disease-specific predictors (e.g., LAS-CF and LAS-idiopathic pulmonary fibrosis). For example, age, which is currently included in the LAS as a continuous variable in the pretransplant model and as a spline at 45 years in the post-transplant model, likely has different thresholds in CF (11). An allocation system that uses population-specific risk factors predictive of wait-list mortality and both short- and long-term outcomes is essential to improve outcomes and aid in patient-centered decision making about transplantation.

Lehr and colleagues have identified objective CF-specific variables that should be considered for inclusion in a revision to the LAS by the Thoracic Committee of the Organ Procurement and Transplantation Network. In parallel, additional work is needed to ensure the accuracy and validity of the LAS-RU-CF. Of note, the LAS-RU-CF is at risk of bias because of missing data. Both the extent and pattern of missing data can bias predictive models. Five of the seven CFFPR variables have a high percentage of missingness. To address this issue, Lehr and colleagues used the "missing indicator method," which assigns an extra variable to the statistical model indicating that the variable is missing. Problematically, this method yields an unpredictable direction and degree of bias; other established methods to address missingness may better mitigate bias (12, 13). Also, the validity of the LAS-RU-CF requires further assessment (14). Models derived from and tested using the same data, as done here, are at risk of overfitting, and assessment and adjustment for overfitting would help establish internal validity. Furthermore, external validity should be established by testing the LAS-RU-CF in a distinct set of patients from a more recent era. As discussed above, to understand the performance of the LAS-RU-CF, these analyses ideally should be conducted only for patients with CF. With these precautions, revisions to the LAS should be considered without delay given the potential of the LAS-RU-CF to reduce the unacceptable wait-list mortality for individuals with CF. ■

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