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EDITORIAL COMMENT

Heart Transplant Allocation

In Desperate Need of Revision*

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Heart transplantation (HTx) remains the best and only causative treatment for patients with end-stage heart failure. This therapy has been enormously successful, with 1-year survival after HTx approaching 90%, and 50% of patients surviving more than 10 years (1). With the current epidemic of heart failure, the number of candidates for HTx listed annually has continued to increase, whereas the number of

See page 1169

available donors continues to stagnate, resulting in an ever-widening supply–demand mismatch (2). This organ donor shortage has further been compounded by the success of long-term mechanical circulatory support devices (MCSDs) that salvage candidates who previously would have died while on the HTx waiting list. However, these support devices are associated with a high rate of complications, including infections, bleeding, thrombosis, and neurological insults, which have an impact on the morbidity and mortality of patients both before and after HTx (3). The percent of patients on mechanical circulatory support at the time of HTx is increasing annually and grew from 5.6% in 1998 to 24.1% in 2011 (4). In some regions of the United States, more than 30% of patients require mechanical bridge to transplantation (4).

The United Network for Organ Sharing (UNOS) was established in 1984 by an act of Congress as a government agency to facilitate the fair sharing of organs within the United States. UNOS has divided the United States into 11 different regions. Each region contains several organ procurement agencies and transplantation centers. The logistics of HTx restrict donor procurement to geographic zones such that the estimated ischemic time will be approximately 4 h or less. Over the years, the allocation system for HTx has evolved. A guiding principle has been the allocation of organs to those in greatest need. Since 1998, the approach to heart allocation has been governed by a 2-tier system that in 2001 was changed to a 3-tier system based on medical urgency (5). With the prolonged waiting list times, a greater percent of transplantation candidates are now prioritized at the highest level of medical urgency (i.e., UNOS status 1A). In 2001, 35% of all transplantations were performed on UNOS status 1A patients; by 2011, the percent of patients transplanted in this category had risen to 56.3% (4). Other factors that discriminate who will receive a donor organ include the accumulated time on the waiting list, human leukocyte antigen cross-match status, body size, and blood type. As an increasing number of patients are listed in the high-urgency category (UNOS status 1A), the current system is less effective in prioritizing donor organs to those in the greatest need. The listing status in the current system is based mainly on hemodynamic compromise and the resulting support (inotropes and MCSDs), which disadvantages certain groups of patients who do not benefit from these therapies, such as those with restrictive, hypertrophic, and congenital cardiomyopathies, malignant arrhythmias, intractable angina, and transplant coronary artery disease. Significant variability in the number of organs available has also developed among UNOS regions (6), such that wait-list times and the use of MCSDs are quite varied.

Singh et al. (7), in this issue of the *Journal*, describe the net survival benefit in patients listed for HTx in the United States on the basis of pre-HTx waiting list mortality and post-HTx survival. Using data from the UNOS database for all patients listed from 2007 to 2010, the investigators stratified the medical urgency during the time on the waiting list for all transplantation candidates. Furthermore, they performed a detailed analysis of survival after HTx for the patients transplanted during this time period. By combining risk for major events including death and delisting due to worsening clinical status before HTx with post-HTx survival, Singh et al. (7) were able to define the overall net benefit of HTx for each of the listed and transplanted patients. Such analysis, not only allows the definition of a patient-specific risk/benefit ratio, but also helps characterize the groups of patients who would benefit most from HTx, with consideration of the demographic, clinical, and laboratory characteristics of each patient. Creating a 10-tier system, the investigators were able to describe 90-day waiting list mortality, which varied from 1.6% in low-risk patients to 19% in high-risk patients. Parameters that predicted pre-HTx mortality during time on the waiting list also predicted post-HTx mortality and included age, etiology of heart failure, need for ventilatory support, renal dysfunction, UNOS listing status, and type of temporary or permanent mechanical support, including intra-aortic balloon pumps. The investigators report an

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increase in post-transplantation mortality in the most critically ill (i.e., high-risk) candidates, yet a statistically significant overall survival benefit was found only in the 3 sickest waiting list risk groups.

The waiting list mortality reported by UNOS is for death while on the list normalized by patient days on the list. Some UNOS analyses report only patient deaths while on the active list and do not include patients delisted as being too ill for HTx. Singh et al. (7) should be credited for providing a more accurate determination of current waiting list mortality by including the deaths of those candidates who are removed from the active list as being too sick for HTx.

The parameters Singh et al. (7) determined as identifying the most urgent and highest-risk candidates—age, renal insufficiency, and need for ventilatory or short-term mechanical support—select those candidates whom many transplantation programs would reject as being too ill for transplantation. With the current organ donor shortage, it is imperative for the transplantation community to identify those patients with the greatest benefit for both short-term and long-term survival. Statistical analysis of large databases also requires careful oversight by physicians to puzzle together the best collection of variables that objectively captures risks and benefits. Singh et al. have begun the process, but input from other data registries such as INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) and careful review of possible prediction models by the heart transplantation community are also required.

There are several limitations to the present analysis. First, it is derived from retrospective data, which although mandatory is not routinely audited. Moreover, data for estimation of waiting list mortality are derived from data entered at 1 point (i.e., the date of initial listing) and do not reflect the subsequent dynamic course of each individual patient. This is of critical importance, as the progression of advanced heart failure in patients on the HTx waiting list is associated, not only with frequent need for pharmacological (inotropes) or mechanical (MCSD) hemodynamic support, which in turn defines UNOS listing status, but also with deteriorating end-organ function, including the kidneys and liver. Nevertheless, this study emphasizes the need for reform in the allocation system to a more objective approach that better serves those who are most in need.

The approach used in the present analysis is analogous to the recently revised lung allocation score, which weighs both the pre-transplantation and post-transplantation risks for recipient selection (8). Similarly, the liver transplantation community has developed a more objective risk score to risk-stratify transplantation candidates (9). Ultimately, using such an approach, time on the waiting list becomes less important for the allocation of organs, which is then based solely on medical urgency and overall survival benefit. Investigators in the Eurotransplant region recently reported an initial comparable attempt based on their listing and outcomes database (10).

It is time for the cardiac community to develop a similar heart allocation score. There has been much discussion about creating such a score. Application of predictive models such as the Seattle Heart Failure Model (11) or the Heart Failure Survival Score (12) in estimating survival in medically managed patients with heart failure can be used, although these models are not accurate in those supported by MCSDs. As the segment of patients awaiting HTx supported by MCSDs continues to rise, the problem of risk estimation in this group will be more critical.

Some investigators have argued that (as it is practiced in the Eurotransplant region) patients bridged with continuous-flow MCSDs be afforded a less acute status because of the recent success of this therapy (13). However, if this approach is adopted in regions most affected by the donor shortage, it seems predictable that in a few years, transplantation lists will consist of patients supported by MCSDs with significant complications (14). As shown again in the present analysis, the risk for waiting with an MCSD as well as the post-HTx survival in these MCSD patients can be significantly affected by the development of comorbid complications (i.e. infection, thrombus, and stroke) (7). Moreover, MCSD patients will benefit from HTx only after MCSD therapy has failed and they have developed life-threatening complications. As the pre-transplantation period is already a harrowing experience for most patients, this time period will be prolonged and made worse by subjecting MCSD patients to a minimum of 2 life-threatening events before transplantation. Therefore, what is needed is a reliable risk model for MCSD patients that can be integrated into the predictive models of patients with heart failure receiving medical therapy. Data from the INTERMACS database in its mandatory reporting phase with the existing UNOS database might serve to create such a prediction model.

Another apparent problem is the geographic variability in waiting list time and physician approaches to patient management in heart allocation, which affect survival and the cost of care. In UNOS regions with longer waiting list times, MCSD use is higher (4). UNOS mandates that patients be informed of center outcomes and overall waiting list time so that they can choose appropriately within and outside their current UNOS regions. Patients with the financial means may opt to enroll in transplantation centers in regions that best suit their needs (i.e., shorter waiting list times, less use of MCSDs). However, not all patients, because of insurance restrictions, have the same opportunity. This is contrary to the founding principles of UNOS, which focused on recipient chance equality.

U.S. transplantation centers have partnered with UNOS to ensure a fair organ allocation system. A recent scandal in liver allocation in Europe illustrated the importance of oversight in organ allocation (15). In more than 4 German centers, inaccurate information was imputed to increase Model for End-Stage Liver Disease scores and increase liver status priority. This resulted in a backlash from the public with a decrease in organ donation, as well as the creation of a government agency similar to UNOS to monitor physician and hospital practices.

The current UNOS heart allocation system is in need of modification to better achieve the original mission of UNOS. Approaches to achieve this goal of fair allocation of organs to the sickest patients while preserving the highest benefits after HTx must be considered. The present study by Singh et al. (7) is a promising first step toward a novel organ allocation system based on distinct risk prediction models that reflect our current medical and surgical treatment options, regional factors, and regulatory limitations.

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