

Heart Allocation Score: A Model Accounting for Waitlist Urgency and Future Success in Orthotopic Heart Transplantation

A. Study Purpose and Rationale

The prevalence of heart failure (HF) has reached epidemic proportions in the United States. There are more than 1 million hospitalizations every year for HF, more than one in nine death certificates mention HF¹, and the lifetime risk of developing HF for both men and women is 1 in 5.² This chronic, progressive disease has a high degree of morbidity and mortality, with recent estimates suggesting that between nearly 10% of all patients with HF have advanced, or stage D, disease³. At this point medical management often becomes inadequate, with orthotopic heart transplantation (OHT) serving as the only definitive treatment option to impact on survival and quality of life.

In the era of immunosuppression, the 1-year post-transplant survival rate has increased from 79% during the period of 1982-1991 to nearly 90% today,⁴ with median survival approaching 11 years.⁵ The improvement in survival and tolerability can be traced to a reduction in rejection rates,⁶ improved management of opportunistic infections, and clearly defined management protocols.⁷ Despite the improvement in tolerability and survival, unfortunately the demand for OHT continues to outpace the supply of available organs. Resultantly, there is a growing number of patients waiting for transplantation. The United Network of Organ Sharing (UNOS) initially developed a system in 1989 attempting to improve organ allocation. UNOS updated the criteria in 1999, which shortened the waiting time and led to a two-thirds mortality decline in the UNOS 1A group awaiting OHT.⁸ Contemporaneously there has been a major shift in the severity of illness of the average candidate listed for OHT, with fewer of the new listings falling in the status 2 category, and the majority being inotrope dependent, necessitating an intraaortic balloon pump (IABP), or a mechanical circulatory support (MCS) device.⁹ The UNOS criteria were again altered in 2007, whereby candidates within a transplant region with 1A or 1B status will be transplanted preferentially, however those with a status 2 designation will not receive the organ before those with status 1A or 1B designation in adjoining geographic regions. The impact of this policy change in Region 9 has been a marked decrease in OHT. At Columbia University Medical Center (CUMC) alone, the average number of annual OHT's has dropped from an average of over 107 per year from 2004-2006 to 88 per year from 2007-2010, with only 39 to date in 2011. This decrease has manifested itself in increased waiting list time.¹⁰

Confronted with the dilemma of a sicker population on a growing waiting list and a continued paucity of available organs, there is an obligation to maximize the impact of each heart transplanted. In 2005, the criteria for lung transplantation was changed when the Organ Procurement and Transplantation Network (OPTN) implemented the Lung Allocation Score (LAS) to prioritize U.S. candidates for lung transplantation by waitlist urgency and transplant benefit.¹¹ Currently the UNOS criteria for OHT focuses more on transplant urgency. We propose to develop a heart allocation score (HAS-9) to predict survival following

heart transplantation and couple that with waitlist urgency to develop a system to allocate organs to those who are the most in need and will derive the greatest benefit.

B. Study Design and Statistical Analysis

This study would involve four main components to develop the HAS-9.

1) Estimation of 1-year HF mortality in patients without MCS device.

This will be accomplished in collaboration with Dr. Wayne Levy, who developed the Seattle Heart Failure Model (SHFM). We will modify the original model to include hazard ratios for inotrope use, mechanical ventilation, IABP's, and refractory ventricular tachycardia. It has been previously demonstrated that the SHFM remains accurate with the addition of IABP, inotrope's, and mechanical ventilation (though they did not test refractory tachycardia and the values were not derived prospectively). However that study was limited in that the REMATCH cohort lack data on diuretic dosing, a key factor in the SHFM.¹² Similar to the original SHFM, the augmentation will be achieved through use of a multivariate Cox model. The model can be developed on the CUMC cohort or the Cardiac Transplant Research Database (CTRD) in addition to being validated on the UNOS data set.

2) Estimation of 1-year mortality for patients on MCS device.

Introducing a MCS device into either the SHFM or the Heart Failure Survival Score has proved to be problematic. As a result, we plan to collaborate with Drs. James Kirklin and David Naftel of the University of Alabama at Birmingham who run the INTERMACS data registry. INTERMACS is a national registry for patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure. Using the data from their 5257 patients, we will model survival based on the type of the device (short versus long term & left ventricular assist device versus biventricular assist device), severity of their disease (INTERMACS level 1-7), and the presence of significant device complication (CVA, the progression of pre-existing or de-novo development of RV failure, human leukocyte antigen (HLA) sensitization, renal insufficiency, device failure or infection [leukocytosis] requiring transplantation, explantation or replacement, gastrointestinal bleeding, age, gender, coagulopathy, thrombocytopenia, and psychological maladjustment).¹³ Like the SHFM, univariate and multivariate Cox models will be applied to analyze the aforementioned factors and their association with 1-year mortality. The INTERMACS database can be separated into a derivation cohort and a validation cohort, allowing for internal validation of the results.

The data set will be sufficiently powered. For example, an estimated 1-year survival based on INTERMACS level alone showed a survival in 65% of INTERMACS level 1 and 72% in INTERMACS level 2.¹³ Based on these numbers, this study will require 44 subjects at each level to have a 90% power and a p value <0.05 with a standard deviation of 10.

3) Estimation of 1-year mortality after transplant.

At CUMC, we have developed a post-transplant model to predict survival based on 769 adult patients that underwent OHT at CUMC from 1999-2010. Through univariate and multivariate Cox proportional analysis of 61 individual characteristics, leading to the identification of key characteristics the predicted success among high-risk patients. These characteristics were assigned values as listed below:

Risk Factor	Criteria	Score
Albumin	² 3.5	2
Repeat transplant	Yes	2
Renal dysfunction	GFR <40	1
Prior CVA	Yes	2
Total CT Surgeries	>2	2
Gender	Female	2

This model has successfully identified high-risk patients (score of ≥ 3) that have a lower post-transplant survival at 1 and 5 years and was validated using the UNOS data set (29,734 patients).

4) Development of an adjustment factor to equalize wait time among certain recipients

There are several known factors that delay transplantation in patients awaiting transplantation. Among them are Type O blood, increased BMI, high levels of anti-HLA antibodies, or sensitization.² Furthermore, there are patients who are ineligible for MCS due to complex congenital diseases, restrictive cardiomyopathy, or right ventricular dysplasia and those with young age who may need to be prioritized. This adjustment factor will be considered after the 1-year mortality and 1-year survival criteria have been established and patients with the above conditions can be analyzed.

The HAS-9 would consist of: (1 year mortality estimate post-transplant – 1 year CHF predicted mortality) – 1 year CHF predicted mortality + Adjustment factor.

C. Study Procedure.

This is a retrospective cohort study using data from patients that have already undergone transplant and those awaiting transplant. There will be no procedures performed or new patient involvement.

D. Study Drugs

Not applicable.

E. Medical Device

Not applicable.

F. Study Questionnaires

Not applicable.

G. Study Subjects

Patients included in this study will be all those that are currently in the INTERMACS database, CUMC Cardiac Transplant Program, UNOS data registry, and the PRAISE1 cohort.

H. Recruitment of Subjects

All patients that will be analyzed in this study are already in databases and their care will not be impacted.

I. Confidentiality of Study Data

Patient's involved in this study are already part of secure databases. These data sets will be kept in password-protected files and will be available only to the investigators.

J. Potential Conflict of Interest

None of the investigators in this study has a conflict to report.

K. Location of the Study

Columbia University Medical Center

L. Potential Risks

None.

M. Potential Benefits

The development of a HAS would lead to OHT in patients who not only display the greatest need for the heart, but those that will derive the greatest benefit from receiving the organ.

N. Alternative Therapies

Not applicable.

O. Compensation to Subjects

None.

P. Costs to Subjects

None.

Q. Minors as Research Subjects

Not applicable.

R. Radiation or Radioactive Substances

Not applicable.

¹ Roger VL, Go AS, Lloyd-Jones DM, et al, for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation*. Feb 1 2011;123(4):e18-e209.

² Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. *Circulation* 2010;122:173-183.

³ American Heart Association. Heart Disease and Stroke Statistics: 2008 Update. Dallas, Tex: American Heart Association; 2008.

⁴ D.O. Taylor, L.B. Edwards and M.M. Boucek, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report—2007. *J Heart Lung Transplant*, 26 (2007), pp. 769–781.

⁵ Aurora P, Edwards L, Christie J, Dobbels F, Kirk R, Kucheryavaya A, Rahmel A, Taylor D, Hertz M. Registry of the International Society for Heart and Lung Transplantation: eleventh official pediatric lung and heart/lung transplantation report: 2008. *J Heart Lung Transplant*. 2008; 27: 978–983.

⁶ J. Lindenfeld, G.G. Miller and S.F. Shakar, et al. Drug therapy in the heart transplant recipient: Part I: Cardiac rejection and immunosuppressive drugs. *Circulation*, 110 (2004), pp. 3734–3740.

⁷ R. John, H. Rajasinghe and J.M. Chen, et al. Impact of current management practices on early and late death in more than 500 consecutive cardiac transplant recipients. *Ann Surg*, 232 (2000), pp. 302–311.

⁸ Current U.S. waiting list for heart transplant candidates: based on OPTN data as of May 4, 2009. Available at:

<http://optn.transplant.hrsa.gov/latestData/rptData.asp> Accessed September 17, 2011.

⁹ Lietz K, Miller LW. Improved survival of patients with end-stage heart failure listed for heart transplantation: analysis of organ procurement and transplantation network/U.S. United Network of Organ Sharing data, 1990 to 2005. *J Am Coll Cardiol*. 2007; 50: 1282–1290.

¹⁰ Heart Transplants Performed at New York-Presbyterian/Columbia: based on OPTN data as of September 9, 2011. Available at: <http://optn.transplant.hrsa.gov/latestData/rptData.asp> Accessed September 17, 2011.

¹¹ T.M. Egan, S. Murray and R.T. Bustami, et al. Development of the new lung allocation system in the United States. *Am J Transplant*, 6 (2006), pp. 1212–1227.

¹² Levy WC, Mozaffarian D, Linker DT, Farrar DJ, Miller LW. Can the Seattle heart failure model be used to risk-stratify heart failure patients for potential left ventricular assist device therapy? *J Heart Lung Transplant*. 2009 Mar;28(3):231-6.

¹³ Lund LH, Matthews J, Aaronson K. Patient selection for left ventricular assist devices. *Eur J Heart Fail* 2010;12:434-443.