HEART FAILURE AND TRANSPLANTATION

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REVIEW:

Donor-recipient matching in heart transplantation

Orthotopic heart transplantation (HTX) is the preferred treatment option for most patients in terminal heart failure. However, there is a growing discrepancy between the increasing numbers of patients on the waiting list and organs available for transplantation in Europe and the United States.[1] Offering the benefits of HTX to a maximum number of transplant candidates therefore requires optimization of donor-recipient allocation and most efficient utilization of available donor organs.[2] A multitude of studies have been conducted analyzing donor and recipient variables to predict post-HTX outcomes. The situation is becoming more complicated by the increasing efforts to enlarge the donor organ pool by utilization of marginal organs.[3] Over the last decade, several scoring systems have been developed with the aim of facilitating a systematic and reproducible organ allocation process leading to optimized post-HTX survival. In this review, we give a concise overview of the current state of knowledge and suggest areas of further investigation.

Prediction of post-transplant outcomes

A large percentage of the literature describes analyses focusing on donor characteristics and their influence on post-HTX outcomes, thereby exploring the acceptable limits of organ quality. As clearly illustrated by Kransdorf and Stehlik, there's consensus within the community regarding the associations of certain donor variables with impaired post-HTX survival, for example increasing donor age or coronary artery disease.[4] However, several donor variables previously considered to be exclusion criteria for organ utilization, including higher-dose norepinephrine donor support, history of cardiopulmonary resuscitation, or reduced left ventricular ejection fraction, have recently been shown not to be inevitably associated with recipient outcomes, thereby offering potential options to safely extend the donor organ pool.[5-7] Integration of knowledge derived by analyses of individual donor variables has led to the development of several donor scoring systems. The Eurotransplant Heart Donor Score (HDS) by Smits et al. incorporates donor age, cause of brain death, compromised history, hypertension, cardiac arrest, left ventricular ejection fraction, valve function, left-ventricular hypertrophy, coronary angiographic findings, serum sodium, norepinephrine and dopamine/dobutamine doses with the aims of predicting donor organ discard and 3-year mortality post-HTX.[8] The donor risk index (DRI) developed from the United Network for Organ Sharing (UNOS)

registry is a 15-point scoring system including ischemic time, donor age, race mismatch, and blood urea nitrogen/creatinine ratio that has been shown to predict 30-day and 5-year mortality following HTX.[9] For the pediatric population, the recently published Pediatric Heart Donor Assessment Tool (PH-DAT) is available. It includes ischemic time, stroke as the cause of death, the donor-recipient height ratio, left-ventricular ejection fraction and glomerular filtration rate and has been shown to be associated with 1-year mortality following pediatric HTX.[10]

On the recipient side, the widely used IMPACT score (Index for Mortality Prediction After Cardiac Transplantation) has been developed from 12 recipient variables including age > 60 years, serum bilirubin, creatinine clearance, dialysis, female sex, heart failure etiology, infection, intra-aortic balloon pump, mechanical ventilation, race, temporary circulatory support, and permanent ventricular assist device. It has been shown to predict 1-year mortality post-HTX.[11]

Incorporating both donor and recipient variables, four more scoring systems have been published. The risk stratification score (RSS) was developed with the use of UNOS data for the prediction of 1-year mortality post-HTX. The score includes 13 recipient variables, 3 donor variables, as well as 2 pairing variables.[12] The International Heart Transplant Survival Algorithm (IHTSA), employing complex non-linear artificial neural networks modeling, combines 32 recipient variables and 11 donor variables and has been shown to predict short- and long-term survival following HTX.[13] A combined recipient and donor score was used by Trivedi et al. for stratification of patients in a retrospective UNOS analysis. The authors demonstrated that allocation of a high-risk donor to a low-risk recipient was associated with acceptable 5-year post-HTX survival, whereas the matching of a high-risk donor to a high-risk or very high-risk recipient led to marginal survival between 65 and 49% at 5 years.[14] The recently published Transplantation Risk Index (TRI) was developed specifically for patients bridged to transplantation by mechanical circulatory support (MCS). It includes 9 recipient and 4 donor variables to aid in decision making for this patient group that is subject to different risks on the waiting list compared with the non-MCS population.[15]

Integration of pre-transplant and post-transplant risk

As demonstrated, the majority of scoring systems has been developed from pre-transplant variables with the aim of predicting the risk of post-transplant mortality. However, the decision of organ acceptance or decline not only needs to be based on the projected post-transplant risk but also needs to incorporate the expected prognosis when remaining on the waiting list. We believe that the available scoring systems give an excellent basement for further studies into the balance of pre-transplant risk and the mortality risk following acceptance of a specific donor organ. The Lung Allocation Score (LAS), published in 2006, is an example of a successfully established score weighing these risks. It was developed for the US lung allocation system and underwent modification before being applied in the Eurotransplant system.[16] The idea behind the LAS is to offer priority to the patients with the worst prognosis on the waiting list but the highest potential for a beneficial course following transplantation. Capturing the idea, a Cardiac Allocation Score (CAS) has been suggested by Smits et al. for the development of a new heart allocation system in Eurotransplant. This study showed that the Heart Failure Survival Score (HFSS) and the Seattle Heart Failure Model (SHFM) both predicted mortality on the waiting list, and that the IMPACT score accurately predicted post-HTX mortality.[17] A combination of those scores was suggested to integrate calculated pre-transplant and post-transplant risks. However, the HFSS and SHFM were primarily not developed for patients on the waiting list for heart transplantation. For the prediction of waiting list mortality, the newly developed

Candidate Risk Score (CRS) was created based on an analysis of the French CRISTAL national registry. It includes short-term mechanical circulatory support (MCS), glomerular filtration rate, bilirubin, and natriuretic peptide and was shown to predict 1-year waitlist mortality.[18]

We believe that more studies are needed investigating the relationship between pre- and post-transplant risks. As an example, a recently published study based on the US Organ Procurement and Transplant Network (OPTN) database demonstrated that patients in urgency status 1A had an immediate survival benefit following transplantation across all donor risk index (DRI) groups, supporting a policy to accept even highest risk marginal organs for patients in the highest urgency status. When receiving a high-risk donor organ, patients in status 1B were shown to have a survival benefit after 12 months, whereas stable patients in status 2 experienced a survival benefit only after 3 years following HTX.[19] This analysis elegantly shows that post-transplant benefit is indeed dependent on the interaction between pre-transplant status and donor organ quality. It would be of interest to investigate sub-strata within the group of patients in stable status 2 and to evaluate the pre- and post-transplant risk balance in other allocation systems with different urgency tiers.

Patients on permanent MCS as bridge-to transplant (BTT) remain to be separately investigated, as this cohort was not included in the development of several of the previously presented scores.[2] The technological advances in the field of MCS have created a viable option to effectively stabilize patients for the time on the waiting list, and the rate of patients transplanted following permanent MCS has reached > 40% in the Registry of the International Society of Heart and Lung Transplantation (ISHLT).[20] A comparison of survival with MCS on the waiting list versus post-transplant survival with a marginal donor heart has shown no significant difference between both groups.[21] However, the effective reduction of patients' risk of death during the time on the waiting list comes at the cost of a non-negligible risk for severe complications, including stroke and life-threatening infection.[22] The proposed new US heart allocation system (Straw Man Model) will bring major changes in the urgency stratification of patients on MCS, the resultant changes in the pre- and post-transplant risk-benefit ratio will be interesting to be evaluated in detail.[23]

Conclusions

Several scoring systems based on donor and recipient characteristics have been proposed for the prediction of post-transplant outcomes. We think that the currently available scoring systems need to be validated using external data sets to evaluate them with regard to their universal applicability in different transplant systems. Ideally, scores based on retrospective analyses should be evaluated in prospective settings. Furthermore, we believe that more studies are necessary investigating the balance between pre- and post-transplant risk to optimize donor-recipient matching and survival after heart transplantation.

REFERENCES:

1. Stevenson LW. Crisis Awaiting Heart Transplantation: Sinking the Lifeboat. JAMA Intern Med 2015;175:1406-9.

2. Kobashigawa J, Khush K, Colvin M, et al. Report From the American Society of Transplantation Conference on Donor Heart Selection in Adult Cardiac Transplantation in the United States. Am J Transplant 2017.
3. Khush KK. Donor selection in the modern era. Ann Cardiothorac Surg 2018;7:126-34.
4. Kransdorf EP, Stehlik J. Donor evaluation in heart transplantation: The end of the beginning. J Heart Lung Transplant 2014;33:1105-13.
5. Angleitner P, Kaider A, Gökler J, et al. High-dose catecholamine donor support and outcomes after heart transplantation. J Heart Lung Transplant, in press.
6. Cheng A, Schumer EM, Trivedi JR, Van Berkel VH, Massey HT, Slaughter MS. Does Donor Cardiopulmonary Resuscitation Time Affect Heart Transplantation Outcomes and Survival? Ann Thorac Surg 2016;102:751-8.
7. Chen CW, Sprys MH, Gaffey AC, et al. Low ejection fraction in donor hearts is not directly associated with increased recipient mortality. J Heart Lung Transplant 2017;36:611-5.
8. Smits JM, De Pauw M, de Vries E, et al. Donor scoring system for heart transplantation and the impact on patient survival. J Heart Lung Transplant 2012;31:387-97.
9. Weiss ES, Allen JG, Kilic A, et al. Development of a quantitative donor risk index to predict short-term mortality in orthotopic heart transplantation. J Heart Lung Transplant 2012;31:266-73.
10. Zafar F, Jaquiss RD, Almond CS, et al. Pediatric Heart Donor Assessment Tool (PH-DAT): A novel donor risk scoring system to predict 1-year mortality in pediatric heart transplantation. J Heart Lung Transplant 2018;37:332-9.
11. Weiss ES, Allen JG, Arnaoutakis GJ, et al. Creation of a quantitative recipient risk index for mortality prediction after cardiac transplantation (IMPACT). Ann Thorac Surg 2011;92:914-21; discussion 21-2.
12. Hong KN, Iribarne A, Worku B, et al. Who is the high-risk recipient? Predicting mortality after heart transplant using pretransplant donor and recipient risk factors. Ann Thorac Surg 2011;92:520-7; discussion 7.
13. Nilsson J, Ohlsson M, Hoglund P, Ekmehag B, Koul B, Andersson B. The International Heart Transplant Survival Algorithm (IHTSA): a new model to improve organ sharing and survival. PLoS One 2015;10:e0118644.
14. Trivedi JR, Cheng A, Ising M, Lenneman A, Birks E, Slaughter MS. Heart Transplant Survival Based on Recipient and Donor Risk Scoring: A UNOS Database Analysis. ASAIO J 2016;62:297-301.
15. Johnston LE, Grimm JC, Magruder JT, Shah AS. Development of a Transplantation Risk Index in Patients With Mechanical Circulatory Support: A Decision Support Tool. JACC Heart Fail 2016;4:277-86.
16. Egan TM, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. Am J Transplant 2006;6:1212-27.
17. Smits JM, de Vries E, De Pauw M, et al. Is it time for a cardiac allocation score? First results from the Eurotransplant pilot study on a survival benefit-based heart allocation. J Heart Lung Transplant 2013;32:873-80.
18. Jasseron C, Legeai C, Jacquelinet C, et al. Prediction of Waitlist Mortality in Adult Heart Transplant Candidates: The Candidate Risk Score. Transplantation 2017;101:2175-82.

19. Nguyen VP, Mahr C, Mokadam NA, Pal J, Smith JW, Dardas TF. The Benefit of Donor-Recipient Matching for Patients Undergoing Heart Transplantation. J Am Coll Cardiol 2017;69:1707-14.
20. Lund LH, Khush KK, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report-2017; Focus Theme: Allograft ischemic time. J Heart Lung Transplant 2017;36:1037-46.
21. Schumer EM, Ising MS, Trivedi JR, Slaughter MS, Cheng A. Early Outcomes With Marginal Donor Hearts Compared With Left Ventricular Assist Device Support in Patients With Advanced Heart Failure. Ann Thorac Surg 2015;100:522-7.
22. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080-6.
23. Meyer DM, Rogers JG, Edwards LB, et al. The future direction of the adult heart allocation system in the United States. Am J Transplant 2015;15:44-54.