Review

The current and future role of artificial intelligence in optimizing donor organ utilization and recipient outcomes in heart transplantation

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Abstract

Heart failure (HF) is a leading cause of morbidity and mortality in the United States. While medical management and mechanical circulatory support have undergone significant advancement in recent years, orthotopic heart transplantation (OHT) remains the most definitive therapy for refractory HF. OHT has seen steady improvement in patient survival and quality of life (QoL) since its inception, with one-year mortality now under 8%. However, a significant number of HF patients are unable to receive OHT due to scarcity of donor hearts. The United Network for Organ Sharing has recently revised its organ allocation criteria in an effort to provide more equitable access to OHT. Despite these changes, there are many potential donor hearts that are inevitably rejected. Arbitrary regulations from the centers for Medicare and Medicaid services and fear of repercussions if one-year mortality falls below established values has led to a current state of excessive risk aversion for which organs are accepted for OHT. Furthermore, non-standardized utilization of extended criteria donors and donation after circulatory death, exacerbate the organ shortage. Data-driven systems can improve donor-recipient matching, better predict patient QoL post-OHT, and decrease needless organ waste through more uniform application of acceptance criteria. Thus, we propose a data-driven future for OHT and a move to patient-centric and holistic transplantation care processes.

Key words: Machine learning, artificial intelligence, cardiac transplantation, organ allocation

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Introduction

Heart failure (HF) is a leading cause of morbidity and mortality in the United States. While medical management and mechanical circulatory support have undergone significant advancement in recent years, orthotopic heart transplantation (OHT) remains the most definitive therapy for refractory HF.

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Public Health Burden of Heart Failure

Heart failure (HF) has been increasing in the United States over time, to an estimated prevalence of 6.2 million, and will increase an additional 46% by 2030 (1). Despite marked improvement in medical therapy, the one-year mortality rate remains high, at 29.6%1. HF long-term mortality has been leveling off, with five-year mortality remaining constant between 2000 and 2010 at approximately 50% (1). In 2019, 80,480 deaths were attributed to HF (up 42.3% from 2007), with costs exceeding $30 billion (1).

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Mechanical circulatory support (MCS) is successfully used to treat some of these patients, with more than 25,000 MCS device implantations for HF between 2006-2017 (1). While great strides have been made in terms of optimal medical management and use of mechanical circulatory support, there remains a need for expansion of orthotopic heart transplantation (OHT) as another treatment modality for patients experiencing refractory heart failure.

Transplantation is a critical solution to heart failure

OHT remains one of the most definitive options for patients with end-stage HF. Since 1982, more than 140,000 OHTs have been performed worldwide (2). Survival post-OHT has steadily improved over time (3). Median survival between 2002 and 2009 was 12.5 years, and 14.8 years in patients who survived the first year (3). Currently, the greatest risk period for OHT patients is the first few months after surgery (3–5), with six-month mortality of 6.4% and one-year mortality of 7.9%. The most significant improvements in survival have been noted within the first year after transplantation, while long-term yearly attrition rate remains unchanged at 3.4% per year (5). Survival to one year depends heavily on the primary diagnosis and indication for transplant, with non-ischemic and ischemic cardiomyopathy having the greatest one-year survival while retransplant has the lowest survival (3). Overall 60% of recipients do not require rehospitalization within the first year and 75% do not require rehospitalization between years two and five post-transplant (3).

Beyond survival, multiple psychological and physical (6) factors contribute to Quality of Life (QoL) post-transplant. This can include number and length of hospital stays, medical interventions, medications, cost of care, patient mobility and strength, and return to work (6, 7). QoL after heart transplant has improved over time, with 70% of patients now having few symptoms in daily living (8). QoL at five years post-transplant is associated with lower mental health measures than the general population, using the SF-36 criteria at one-, three-, and five-years post-transplant (6). Older patients tended to have a higher QoL post-transplant, while depressed patients had lower scores in all SF-36 domains6. Predictors of lower QoL score include pain, sexual dysfunction, gastronitestinal symptoms, younger age, and higher New York Heart Association classification (6). Despite improved functional capacity, only 27% and 38% of recipients return to work at one- and five-years post-operatively, respectfully (8).

Inequalities in donor organ allocation restrict patient access to cardiac transplantation

In October 2018, the United Network for Organ Sharing (UNOS) approved new criteria for OHT allocation, giving priority to patients who were sickest, with the aim to reduce waitlist mortality. Thus far, the recent changes have dramatically altered the use of bridging strategies prior to transplantation (9, 10). Patients are now less likely to be supported with left ventricular assist device (LVAD) and more likely to be temporarily supported by intraaortic balloon pump (IABP) (9). This has also led to an increase in patient`s hospital length of stay pre-transplant, but decreased days on the waitlist overall (9). Post transplantation outcomes appear to be similar prior to implementation of new allocation strategies (10). Additionally, patients who are stable on LVADs as bridge-to-transplant therapy, are increasingly unlikely to receive OHT (9). Finally, UNOS policy allows a 30-day window for patients with a durable LVAD to be elevated to Status 3, with the potential to strategically use a patients 30-day window to increase their chances of receiving an OHT (11).

Relative shortage of donor organs limit heart failure potential

The single greatest issue facing OHT is that more than 50% of offered donor hearts are not accepted for transplantation, usually being rejected due to strict donor selection criteria (10, 12–14). Of the 12,588 hearts offered for transplantation during 2020, only 3,658 transplants were performed (15). Frequently, these reasons result from clinicians' interpretation of organ suitability and hesitancy to accept a perceived higher risk organ for fear of regulatory consequences if a negative outcome occurs (12). Donor heart acceptance criteria lack standardization and are often determined using small sample size studies (14). In fact, current data suggest that recipient factors more accurately predict survival post-transplant than donor factors (16).

Recent increases in utilization of extended criteria donor (ECD) hearts may alleviate the shortage of transplantable organs. Criteria for defining the new ECD organs include age >40, LVEF <60%, >500-mile distance away, >50 previous center refusals, and positive HIV, HCV, or HBV (10).

The only criteria significantly associated with a negative survival outcome at high-volume centers is donor age >40 (10).

Current donor-recipient matching includes size, weight, blood group, HLA antibodies, and variable center-specific criteria. Donor demographics, including size, sex, and age, as well as comorbidities such as hypertension, diabetes mellitus, and smoking all are associated with an increase in post transplantation mortality (17, 18). Size matching is a useful adjunct to blood group and HLA antibodies, as significant under-sizing of greater than 30% increases the risk of all cause one-year mortality by approximately 30%, while conversely, insignificant risk was seen with over-sizing (19).

The majority of OHTs are performed using organs procured from donation after brain death (DBD) donors (20). While there exists potential to improve utilization of DBD hearts, further exploration of alternative donation sources is required to fully alleviate the donor organ shortage. Donation after circulatory death (DCD) is one avenue in which the pool can be significantly increased. Early transplantations utilized DCD organs, but the practice fell out of favor following the acceptance of brain-death criteria (20). DCD remains a complex issue, requiring advancements in ex vivo preservation and testing, as well as widespread adoption to emerge as a viable option for increasing organ pool. Some countries have adopted a more liberal use of DCD organs in select transplantation patients, reporting short-term survival similar to DBD organs (21). Data currently suggests that potential number of organs from DCD donors is rising faster than those available from DBD donors, although a proportion of DCD organs will be nonviable for OHT (21). The potential increase in viable OHTs by fully implementing DCD organ utilization is approximately 30% (21). Therefore, there is room for optimization of donor-recipient matching, which can significantly decrease the number of discarded donor hearts.

Expansion of ECD, DCD, and improved donor-recipient matching can increase the pool of donor hearts available for OHT. However, widespread implementation remains a challenge. For the transplant director, integrating not only the typical characteristics, but also adding ECD, DCD, and additional matching criteria poses a unique challenge. Artificial intelligence can serve to assist with some of these challenges by predicting patient outcomes given various donor-recipient characteristics and can easily integrate the added complexity of additional risk criteria.

Metrics for comparing transplantation center outcomes require modification

Centers for Medicare and Medicaid services (CMS) have established short-term minimum outcomes required for center certification and funding, which influence clinicians' decision as to whether accept a heart for transplantation (22). Significant risk aversion arises over potential regulatory intervention for centers with lower 90-day and one-year survival rate. However, the practice of OHT and organ allocation involves more nuance than a strict donor guideline can provide.

OHT centers have significant differences in short-term outcomes (3, 23). Low-volume centers have lower one-year patient and graft survival across all donor-recipient pair risk stratification (3). All centers performing more than 40 transplants per year have a 30-day mortality of less than 5% (7). Substantial intercenter variance appears to be reduced once a volume of 20 transplants per year is achieved (23). Centers with higher volume also have a greater utilization of ECD organs, and have shown one- and five-year survival to be equivalent to non-ECD hearts (10). Thus, high volume centers can continue to undertake increased transplantation using ECD hearts, and further expansion of ECD criteria could aid in supplementing the suitable donor organ supply. Centers with low volumes often have worse outcomes for patients on the waiting list (23). The CMS requirement for accreditation is 10 transplants per year, however 65% of centers failed to achieve this value (24). Low-volume centers performing less than 10 transplants per year have up to a 100% increased risk in 30-day mortality, and centers performing fewer than two per year have a 115% increased 30-day mortality (23). Additionally, a single poor outcome has a greater effect on a low-volume center’s short-term survival, further disincentivizing the use of potentially marginal organs. Due to regulatory oversight and requirements to maintain specific, albeit arbitrary, survival rates, low-volume centers may be encouraged to practice an excessively conservative acceptance criteria for donor organs (12, 22).

In summary of the current state of OHT, many potential hearts are needlessly discarded which would have provided improved patient quality of life and extend survival.

There is variation in outcomes between high- and low-volume centers, and organs procured via ECD as well as DCD. These organs have the potential to alleviate some of the imbalance between supply and demand but are inherently higher risk and should thus be undertaken at centers familiar with these procedures.

Additionally, transplant directors may be reluctant to undertake significant ECD and DCD transplantations given the perceived risk. These challenges can be addressed by the development of an artificial intelligence (AI) application which aids in the decision-making process, ideally, leading to the utilization of more high-risk organs to better address the donor organ shortage.

Overview of artificial intelligence for improving outcomes in OHT

Artificial Intelligence (AI) is the extension of machine learning (ML) that seeks to mimic and enhance the decision-making process of humans by leveraging big data and computational efficiencies. While these terms are often used interchangeably, they do have key differences. Understanding these differences and subsequent application to medicine is important for further implementation.

AI refers to a broad overview of all systems or technology which can perform various human-like tasks (25, 26). ML refers to a specific category within AI that utilizes large data sets to learn from, improve task-efficiency, and develop educated predictions (26). Deep learning (DL) algorithms are emerging and have potential to revolutionize medical decision making, but few physicians have experience with them. DL is more complex and attempts to develop an artificial neural network (26), though the specific algorithms are beyond the scope of this review. In general, all three require the utilization of significant computing power and specific training to integrate vast amounts of data in a more efficient manner than humans can perform (25, 27).

Within the medical field, AI is already being utilized, with applications ranging from disease diagnostics to drug dosage algorithms (28). The advantages of implementing AI include medical efficiency, precision, economic, and decreased physician workload. With respect to medical accuracy, AI has been on par or outperformed humans in making accurate medical decisions (28–33). In a study from Stanford University, deep neural networks were able to achieve equitable performance as 21 board-certified dermatologists on biopsy proven clinical images (29). The Society of Thoracic Surgeons has developed an online adult cardiac surgery risk model, with remarkable success in prediction of performance metrics (30, 31). Known incidence of acute kidney injury after cardiac surgery has led to the development of a ML program to predict its post-operative incidence (28). The use of AI within OHT has been used to predict survival at various time-points both pre- and post-OHT (34-40), identify variables that predict waitlist mortality (41) and predict graft rejection using histopathology (42) (Table 1). However, the use is not widespread, and most studies have evaluated retrospective data with no reported use in prospective selection of donor-recipient pairs that we could find. A recent systematic review by Naruka et al. identified three primary roles of ML in OHT: 1) Predictive modeling of OHT outcomes, 2) ML in graft failure outcomes, and 3) ML to aid imaging in OHT (43). Their results also suggest that ML is not limited to morbidity and mortality prediction, but could assist with identifying graft failure, medication adherence, and lifestyle changes in OHT patients (43). The continued application of AI within the realm of OHT has the potential to decrease inherent biases present when evaluating potential donor-recipient pairs, while using statistics and modeling to accurately match donor-recipient pairs to optimize short- and long-term recipient outcomes in addition to patient-centric QoL.

Implementation of ML to drive precision heart transplantation

The implementation of ML in OHT remains in its infancy, with no direct applications to the field (27). Limiting factors to full application of AI have been discussed by Goswami and include four critical components which are necessary for optimal integration: 1) data scientists with expertise and experienced in AI, 2) quality and volume of available data, 3) experience of clinical faculty in transplantation, and 4) assessment of biases (27).

ML has the potential to improve the process by which organs are accepted for OHT, as it can integrate large data sets, such as those from: UNOS, Organ Procurement and Transplantation Network, Scientific Registry of Transplant Recipients, and genetic registries to predict short- and long-term outcomes given an algorithmic matching program. Utilizing statistical and neural network modeling, ML has been able to better predict long-term outcomes in liver and kidney transplantation than current practice standards (32, 33) Retrospective survival predictions for OHT patients have also been successfully demonstrated with high accuracy, though not universally implemented (44).

Table 1: Review and comparison of select studies using various techniques of artificial intelligence in cardiac surgery

Author	Population	Design	Follow-Up	Results	Outcomes
Medved et al[34]	27,860 adult heart transplantations	Derivation cohort (pre-2009) and test cohort (post-2009) to compare neural network IHTSA vs traditional risk model IMPACT	One-year mortality	Flexible nonlinear artificial neural network (IHTSA) predicts one-year mortality with better accuracy than traditional risk scoring (IPACT)	Public web-based batch calculator available for virtual recipient-donor matching pool
Yoon et al[35]	UNOS database of 59,820 patients who received heart transplant and 35,455 patients on the weight list who did not receive heart transplant	Development of novel risk prediction algorithm using ToPs	Three-year mortality	ToPs improve survival prediction in both pre- and post-cardiac transplantation	ToPs predict survival with more accuracy and more personalization which benefits patients, clinicians, and policymakers for clinical policy and decision making
Miller et al[36]	UNOS database of 3,502 pediatric patients undergoing heart transplant	Evaluation of three machine learning algorithms (classification and regression trees, RFs, and ANN)	One-, three-, and five-year mortality	RF achieved the best fit to training data, and performed best in testing data; however, sensitivity was poor across all models	ML demonstrates fair predictive utility with poor sensitivity, potentially fundamentally limited by determinants of long-term survival missing from registry data sets
Zhou et al[37]	381 patients undergoing heart transplant at a single institution in China	Development of risk-reduction model using least absolute shrinkage and selection operator	One-year mortality	Albumin, recipient age, and left atrial diameter three most important factors in one-year mortality prediction. RF models achieved best sensitivity in predicting survival	Prediction model for postoperative prognosis that could help to recognize high-risk recipients, personalize therapy, and reduce organ waste
Allyn et al[38]	6,520 patients undergoing elective cardiac surgery with cardiopulmonary bypass	Retrospective comparison of machine learning vs EuroSCORE II	Prediction of in-hospital mortality	Machine learning is superior to EuroSCORE II in predicting mortality after non-urgent cardiac surgery	Machine learning can be beneficial in the field of medical prediction.
Agasthi et al[39]	ISHLT registry of 15,236 patients undergoing heart transplantation	Included 87 variables in GBM model	Five-year survival and graft failure	Variables with highest predictive value included length of stay, recipient and donor age, recipient and donor BMI, and total ischemic time	GBM can provide good accuracy in predicting both five-year mortality and graft failure after heart transplant, and may aid in selecting matches for transplant with high likelihood of success
Ayers et al[40]	UNOS registry of 33,657 patients undergoing heart transplant	Retrospective, randomized controlled trial combining multiple machine learning algorithms into one ensemble model	One-year survival	Ensemble model demonstrated superior predictive performance	Machine learning can improve risk prediction, which may assist with patient selection, evaluation of transplant centers, organ allocation, and preoperative counseling and prognostication

Artificial Neural Networks (ANN); Gradient boosted Machine (GBM);International Heart Transplantation Survival Algorithm (IHTSA); Index for Mortality Prediction After Cardiac Transplantation (IMPACT); International Society of Heart and Lung Transplant (ISHLT); Trees of Predictors (ToPs); Random Forests (RFs); United Network for organ Sharing (UNOS)

While survival prediction alone is useful, it is insufficient without improved donor-recipient matching and a focus on patient-centric outcomes. Better donor-recipient matching will provide guidance to the physician as to whether donor organ is appropriate risk for a specific recipient, and likely to improve that patient's QoL.

ML can integrate patient centric QoL data into models that optimize patient outcomes, in addition to compatibility algorithmic matching. Using ML, algorithms can be trained to predict if a given patient will survive to 90 days, one-year, or to whether survival will be meaningful and worth the risk of OHT. Additionally, in the era of implantable and wearable medical technology, ML offers the promise of near real-time monitoring of continuously monitored patient data that is not classically considered in medical care. One can imagine a world in which post-transplantation patients have a medical device constantly monitoring their cardiac function. An alert could then be sent to patients and/or their clinicians when abnormalities occur. Ideally, this would decrease the cost associated with excess hospitalizations post-transplant, as complications could be detected and addressed early, before requiring hospitalization. Further, when intervention is warranted, decreased time from event to care will lead to greater recovery. The nature of computational systems lends to improvement over time. Thus, we believe the future is bright for AI to improve outcomes in OHT.

Conclusion

In summary, OHT is a lifesaving and life-changing procedure, but the field is focused on short-term procedural outcomes rather than a holistic QoL. Patient-centric approaches will enhance long-term outcomes and organ utilization. The combination of algorithmic matching between donor and recipient via ML may serve to maximize long-term patient and graft survival. ML may encourage physicians to accept more marginal donor organs if presented with concrete and justifiable data suggesting that the organ is of appropriate survival risk for that recipient. This can further expand the pool of donor organs and decrease the number of discarded organs, thereby decreasing waitlist morbidity and mortality. Additionally, integrating donor-recipient matching with patient-centric outcomes using ML may help predict post-OHT QoL in metrics meaningful to patients. Development of an integrated model of the recipient for estimating short- and long-term risk, as well as QoL using a data-driven advance towards precision OHT will deliver greater value to more patients, while decreasing needless waste and excess risk aversion.

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Waterfall in Bardonecchia, Italy 2022. Photography by Jasom Winder, London, UK