A DATA-ANALYTIC APPROACH TOWARDS INCREASING DONOR HEART UTILIZATION IN THE UNITED STATES

by

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ABSTRACT

SAGAR SATYANARAYANA. A Data-Analytic Approach Towards Increasing Donor Heart Utilization in the United States. (Under the direction of DR. GABRIEL ZENAROSA)

Heart transplantation is the best option available to treat end-stage Heart Failure (HF). There is a shortage of donor hearts in the United States even with the steady increase in the number of donors. One likely reason is the decreasing transplant wait-list mortality resulting from advancements in bridge-to-transplant (BTT) therapies in HF, which causes the candidates to be more selective of donor hearts offered. This study aims to evaluate the changes in the donor characteristics between two decades (1995–2005 and 2005–2015), separated by dramatic increase in BTT.

UNOS deceased-donor data was used for the study and divided into two decades with respect to the donor date (1995–2005 and 2005–2015). Two logistic regression models of donor characteristics were derived for the above two decades and used to decide whether an organ is discarded or not. These two models are compared on the actual donor data for 2005–2015. Model 1 (1995–2005) had 5,840 fewer discards than Model 2 (2005–2015). Organs deemed transplantable from two models were simulated using Thoracic Simulated Allocation Model for organ allocation and acceptance.

The transplant rate for Model 1 is significantly higher than the Transplant rate for Model 2 at the high-priority status 1A and is not significantly different in lower priorities 1B and 2. However, there was no statistical difference in the mortality rate between the two models in Status 1A.

The better performance of Model 1 over Model 2 in both transplant and mortality rates implies that hearts admissible for transplantation are being discarded. The donor-heart quality preferences of transplant candidates for accepting offers are becoming stricter, and is contributing to the donor-heart shortage in the United States.

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LIST OF ABBREVIATIONS

BMI Body Mass Index. 16, 22, 27

BTT Bridge-To-Transplant. 1, 2, 7

CPR Cardiopulmonary resuscitation. 16, 27

CVA Cerebro-Vascular Accident. 13, 15

DHHS Department of Health and Human Services. 4

ECD Extended Criteria Donors. 2, 4, 7, 20

HF Heart Failure. 1

HTx Heart Transplantation. 14

LVAD Left Ventricular Assist Device. 7

MCSD Mechanical Circulatory Support Device. 1–3, 7, 21, 37, 40

OPO Organ Procurement Organization. 4, 5, 9, 20, 38, 40

OPTN Organ Procurement and Transplantation Network. 4, 17, 30, 37

ROC Receiver Operating Characteristics. 24

SRTR Scientific Registry of Transplant Recipients. 8, 17, 37, 39

TSAM Thoracic Simulated Allocation Model. 2, 3, 8, 11, 17, 20, 29, 30, 39

Tx Transplantation. 18

UNOS United Network for Organ Sharing. 2, 4, 17

CHAPTER 1: INTRODUCTION

Heart Failure (HF) is an important contributor to both the burden and cost of national healthcare expenditures, with older Americans hospitalized for HF more than for any other medical condition [1]. With the aging of the population, the impact of HF is expected to increase substantially [2, 3]. Heart transplantation remains the best option for patients with advance heart failure for long-term survival [4, 5].

There is a donor heart shortage in the United States: the number of hearts transplanted has remained stagnant at 2,500 transplants every year for the past decade (2005–2015) [6]. Despite the fact, that the number of donors kept increasing steadily from 2005 to 2015, with an overall increase of 35% from the previous decade (1995–2005) [7]. The donor heart acceptance rate however, has decreased from 44% in 1995 to 32% in 2010 [6]. The number of total donor hearts discarded between 2005–2015 has risen from 42,476 to 63,431 discards between the years 1995–2005. One likely reason for the rising numbers in discards can be attributed to the increasing use of Mechanical Circulatory Support Device (MCSD) as a bridge to transplantation [8].

The field of circulatory support has matured dramatically in the recent years [9]. The evolution of continuous flow MCSD from pulsatile-flow left ventricular assist devices resulted in improved wait-list survival and quality of life in patients supported with Bridge-To-Transplant (BTT) therapy [10, 11, 12]. A total of 218 patients on the wait-list were on MCSD support from 1995–2005 whereas, 6,220 patients used MCSD as a bridge to transplant from 2005–2015.

The use of MCSD as a bridge to transplant, would mean that the patients bridged with a device would have lesser wait-list mortality, allowing them to wait for preferred donor hearts instead of accepting marginal quality hearts [13]. These marginal

quality hearts or Extended Criteria Donors (ECD), have traditionally been believed to have poor post-transplantation outcomes. However, recent studies show very little association between donor characteristics and post-transplantation outcomes [14]. Patients with MCSD have a 30-day grace period to stay on the high-priority Status 1A [13, 15, 16, 17, 18], even though there was no difference in post-transplantation survival between Status 1B and Status 1A under the grace period [19]. This implies that donor hearts offered to high-priority status patients has a high likelihood of not being accepted by the recipients. The limitations in cold storage system makes it hard to offer these declined hearts to patients having lower priority on the wait-list, resulting in the discard of donor hearts which could otherwise be transplanted to a more-willing patient in other priority statuses and/or in other regions. BTT therapy, thus, led to changes in transplant wait-list prioritization and induced some patient selectiveness, which led to an increase in donor heart discards.

It should be noted, however, that donor quality characteristics are not the only reason to discard a heart. Other reasons like no suitable recipient, organ refused by the program, donor medical, and social history may lead to the decision to discard [7].

The objective of this study is to evaluate the changes in donor characteristics with which a heart was discarded between the two decades (1995–2005) and (2005–2015). We develop two donor-heart accept/discard decision models corresponding to two decades through which we provide evidence that hearts discarded in the second decade (2005–2015) have higher thresholds for quality than those discarded in the first decade (1995–2005). We further demonstrate, using the Thoracic Simulated Allocation Model (TSAM) [20], that the decision model for the first decade used in the second decade leads to an improvement in donor heart allocation, specifically monotonic increases in transplantation and mortality rates.

The thesis is organized as follows

- Chapter 2: Literature Review. This chapter contains literature on United Net-

work for Organ Sharing (UNOS) donor selection and heart allocation policies and its evolution after the advent of MCSDs, assumptions and basic approaches of TSAM and Predictors for donor heart utilization in the United States.

- Chapter 3: Methods. This chapter describes the selection of study population and the various methodologies used in the study.
- Chapter 4: Results and Discussion. This chapter includes simulation results from TSAM and discusses its implication for the study.
- Chapter 5: Conclusion. This chapter summarizes this thesis and discusses the limitations and future scope of the study.

CHAPTER 2: LITERATURE REVIEW

2.1 Donor Selection and Organ Allocation

Because of the scarcity of donor organs, it is imperative to maximize the utilization of suitable available organs. The assessment of donor quality for heart transplantation remains an area of controversy and investigation [21]. UNOS serves as the Organ Procurement and Transplantation Network (OPTN) through its contract with the Department of Health and Human Services (DHHS) it is charged with ensuring fair and equitable allocation of organs in the United States [22]. The US congress passed the National Organ Transplant Act in 1984, creating OPTN and Organ Procurement Organization (OPO). In 2000 DHHS issued a final rule which is still the primary regulation governing OPTN/UNOS. Stressing on equitable regional distribution and the severity of the recipient's illness. Recent developments like

- The increase in candidates awaiting transplantation with a proportional increase in the available donor hearts;
- Higher than desirable waiting list mortality rates in severely ill patients (Status 1A), and ;
- Increased utilization of mechanical support devices in the wait-listed patients

have made it impetus to review heart allocation systems. A heart sub-committee with members from UNOS board was created to review and improve the existing allocation policies. In 2005, a three-tiered allocation system was started with broader organ sharing. This change led to the substantial decrease in wait-list mortality for Status 1A and Status 1B candidates. Donor utilization rate is decreasing each year even after many centers expanded their donor pool by considering older donors and ECD. Due to the availability of stable volumes of donor hearts and increased public

scrutiny many OPO have adopted a risk-averse donor utilization scheme [21].

2.1.1 Zones

Depending on the distances between the donor's OPO and the recipient's location, the recipient's wait-list is categorized into six zones as listed below.

- **Local** - Same OPO
- **Zone A** - within 500 miles
- **Zone B** - within 1,000 miles
- **Zone C** - within 1,500 miles
- **Zone D** - within 2,500 miles
- **Zone E** - further than 2,500 miles

2.1.2 Heart Medical Status

A priority status is assigned to all patients in the wait-list depending on their current medical conditions.

- **Status 1A** - Includes critically ill patients who require continuous high-dose inotropic drug therapy or mechanical assistance, if that mechanical assistance is less than 30 days in place, has a device-related complication, is a total artificial heart or is mechanical ventilation. Patients with an urgency and potential for benefit.
- **Status 1B** - Includes medically stable patients who require continuous inotropic drug therapy or mechanical assistance.
- **Status 2** - Includes patients with chronic heart failure who do not meet the higher urgency criteria for Status 1A or 1B listing.

The allocation schemes for 1999–2005 and 2005–present are shown in the Table 2.1.

Table 2.1: Heart Allocation Scheme: In Hierarchical Order

Adult Heart Allocation 1999–2005	Status on wait-list	Adult Heart Allocation 2005–present	Status on wait-list
Local	Status 1A	Local	Status 1A
	Status 1B		Status 1B
	Status 2		
Zone A	Status 1A	Zone A	Status 1A
	Status 1B		Status 1B
Zone B	Status 1A	Local	Status 2
	Status 1B		
Zone A	Status 2	Zone B	Status 1A
			Status 1B
Zone B	Status 2	Zone A	Status 2
Zone C	Status 1A	Zone B	Status 2
	Status 1B		
			Status 2
Zone D	Status 1A	Zone C	Status 1A
	Status 1B		Status 1B
	Status 2		Status 2
		Zone D	Status 1A
			Status 1B
			Status 2
		Zone E	Status 1A
			Status 1B
			Status 2

2.2 Evolution and Effects of Mechanical Circulatory Support Devices on Heart Allocation Policies

The modern era of cardiac surgery began in 1953 with the first clinical use of cardiopulmonary bypass, allowing increasingly complex operations and laying the foundation for circulatory assist devices [23]. Shortly after its invention, the heart-lung machine began to be used to support patients with post-cardiotomy cardiogenic shock to facilitate recovery after failed operations. The first clinical use of an implantable artificial ventricle was reported by Liotta et al. [24] in 1963. The pump provided partial left ventricular bypass for four days after postoperative cardiac arrest before the patient died of multi-organ failure [24]. After nearly 50 years of clinical development, durable MCSDs are widely available for patients with advanced heart failure. The field of circulatory support has matured dramatically in recent years, thanks to the advent of smaller rotary pumps [25]. The evolution of continuous-flow MCSD from pulsatile-flow left ventricular assist devices resulted in improved wait-list survival and quality of life in patients supported with bridge-to-transplant(BTT) therapy [10].

The percentage of patients bridged with MCSD increased from 19% in 2001 to 64% in 2010 while the number transplanted during their 30-day 1A grace period declined from 57% in 2005 to 16% in 2011—that is, 84% of BTT patients in 2011 needed more than 30 days 1A time to be transplanted. Despite being older, less favorable recipients, these patients spent more time in status 1A [18] even though there is no significant differences in post transplantation survival between Left Ventricular Assist Device (LVAD) patients transplanted as UNOS 1B, 1A grace period or for a device complication and had greater wait-list survival than patients without BTT therapy [13]. This allows patients to receive preferred donor hearts, which has resulted in a significant drop in the heart utilization rate as marginal quality hearts or ECD which are traditionally considered to have poor post-transplantation outcomes are viable to use only in some regional patients due to limitations in cold-storage. However, donor

acceptance criteria may have very little effect on post-transplantation outcomes [14]. Although LVAD technology was pioneered in the bridge setting where transplant offered a bailout for device failure as devices matured, development began to be targeted toward devices capable of long-term or permanent circulatory support [26].

2.3 Thoracic Simulated Allocation Model

TSAM is a computer simulated program developed by the Scientific Registry of Transplant Recipients (SRTR) to simulate the allocation of hearts and/or lungs to candidates waiting for thoracic organ transplants and their outcomes [20]. The program has been designed to support studies of alternative organ allocation policies. It can also use a variety of allocation rules to determine how a series of thoracic organs would be allocated to a list of potential recipients under each of the rules considered. The allocation process involves some random components reflecting the uncertainty in acceptance decisions when an organ is offered to a potential recipient and reflecting the unpredictable life expectancy that can result from receiving a transplant or not. In order to account for such random variation, the program can also make organ allocations several times with the same set of allocation rules, candidate lists, and organs in order to determine what happens on average.

2.3.1 Basic Approach and Random Processes

TSAM simulates the organ allocation system with an event-sequenced Monte Carlo technique. Some of the modeled processes are random in nature, and the model samples pseudo-random numbers to simulate a realization of processes over the specified time period. Each such realization of the organ allocation system constitutes a single replication.

2.3.2 Simulation Assumptions

- Arrivals of candidates are input to the model with a data file.
- The initial wait list is input to the model with a data file.

- An entire history of wait-list status changes (to the end of the Allocation Run, death, or removal from the wait-list) must be input to the model for each patient (medical urgency status changes, time of removal, and time of death). This is the history that will be used for the patient up until the time (if any) that the patient is allocated a transplant during the simulation. Note that this history does not specify the time of a transplant. This history can be based on actual experience, although a hypothetical history must be prepared for transplanted patients to tell what would have happened to them had they not received a transplant. Alternatively, the histories can be based on data generated from hypothesized models.
- Once a candidate receives an organ, that patient's input stream of status changes no longer applies. If the patient re-lists, the model assigns a status change history to the patient by randomly selecting a set of status changes from a pool of user-defined histories specifically provided for this purpose.
- The values of several other parameters are specified in the program or tables and remain constant during a run. These include the parameters of the graft failure time distribution and the geographic membership relationships among institutions, local units (OPOs), and zones. For example, it is assumed that patients do not move among institutions, and institutions do not change affiliation with OPOs. Because these parameters and relationships are controlled by input data, they can vary from case to case.

2.3.3 Organ Acceptance and Post-graft Survival

- Organ Acceptance: The user defines a calculation used to compute the organ acceptance probability. Values that may be used in this calculation are scalar variables, characteristics of the organ or donor, characteristics of the potential organ recipient and/or values that are calculated from characteristics of the specific organ and patient combination under consideration. For each patient

to whom the organ is offered, this calculation is performed, and the resulting value, X, is transformed using an inverse logit transformation $\frac{exp(x)}{1+exp(x)}$. That value is then compared to a random number between 0 and 1. If the random number is less than this value, then the organ is accepted, otherwise it is refused. An organ is said to have been discarded after it is either offered to all potential recipients (up to the maximum organ offer count specified on the Acceptance Definitions panel) and each of those offers has been refused.

- Post-Graft Survival: Post-graft survival is also specified by the user in the model. The user defines a calculation which is then used to determine the patient's death date after a transplant. The calculation, once again, may be made up of scalar variables, organ characteristics, patient characteristics, and/or calculations that depend on information from both the organ and the patient. Each time a transplant is performed in the model, this calculation is performed and the resulting value is combined with a random number, the result of which is used to determine the death date, using the method chosen by the user - either a Cox proportional hazard model or a Weibull distribution. A set of possible outcomes and their relative probabilities is associated with each death date. The possible outcomes are re-listing at differing times prior to the death date and with differing medical characteristics, or not re-listing.

2.3.4 Event Handlers

- Organ Arrival Event: This event handler selects a candidate to receive the organ that has become available. It applies the allocation rules that have been defined in the model. It performs the match run by reordering the wait list according to the rules and offering the organ to candidates in order. It simulates the organ acceptance process by sampling from a uniformly distributed random variable and comparing this to the probability of acceptance, which is calculated using acceptance inputs to the model. If no candidate accepts the organ, the organ

is discarded. If the organ is accepted, the event handler removes the recipient from the wait list. Whatever the outcome, the event handler writes a record with the results of the match run.

Heart-lung candidates are on both the heart waiting list and the lung waiting list. The allocation rules for a combined heart-lung package allocate to either the heart list or the lung list, depending upon the heart-lung allocation rules which are input to TSAM. If the patient who accepts the organ package needs both the heart and lungs, they get both. If they need only a heart, for example, they take the heart and the remaining organ(s) become the next organ allocation. If the organ package being offered includes only a heart, it is offered to the heart list excluding heart-lung candidates. If the organ package includes only a lung (or double lungs), it is offered to the lung list excluding heart-lung candidates. The event handler places the recipient on a list of graft recipients and schedules a death event for the recipient. It uses the model (as described in Chapter 4) to determine a possible outcome prior to death and the time that will elapse until this outcome. It then schedules the outcome events, which could include a re-listing and possibly some post-graft status change events. Please note that these status change events are defined differently in the model from those that take place prior to transplant. The latter are described next.

- Status Change Event: The status change file contains records that describe the medical status history of every wait list candidate from the time of the candidate's arrival to the model (either the initial wait list snapshot or arrival to the wait list) until the candidate's death. This history is valid until such time as the candidate may receive a graft. If a transplant recipient re-lists, the recipient's status history is provided by a different source. Whichever source of status changes applies, the model invokes the status change event handler when a status change event occurs.

If the candidate's medical status has changed, the model updates variables that keep track of the time that the candidate has been in the previous medical status. The event handler updates the candidate's medical status to the new value and updates other variables that keep track of status occupancy time.

If the new status is 9 (removal), the event handler removes that candidate from the wait list and places the candidate on a list of removed patients. If the new status is 8 (death), the event handler removes the candidate from the wait list and writes an outcome record for the patient. If the patient dies after removal from the wait list, the model removes the patient from the list of living removed patients.

- Candidate Arrival Event: This event occurs when a patient joins the wait list. When this happens, the event handler places the patient on the wait list and initializes all descriptions of the candidate (e.g., demographic descriptors, medical status, previous transplantation status, and institution where listed).
- Post-Transplantation Events: When a patient receives a graft (i.e., at the time of an organ arrival event), the simulation samples the future time of graft failure and determines whether the patient will re-list or not. The simulation accordingly schedules the patient's death and, potentially, the re-list event. The event handler for post-transplantation events processes these events.

  In the case of a death event, the event handler removes the patient from the list of living graft recipients and writes an outcome record. In the case of a re-listing event, the simulation removes the patient from the list of non-wait-listed graft recipients and adds the patient to the wait list. A status change history was already selected for the patient at the time of the organ arrival event, and the event handler initializes the patient's medical status to the initial set of values provided in this history.

2.4 Donor Predictors of Allograft Use and Recipient Outcomes After Heart Transplantation

Khush et al. [27] sought to identify the predictors for graft discard and to determine if these characteristics has an adverse effect on post-transplantation survival. Eleven donor risk factors for allograft non-use were selected a priori, based on previous literature. These included:

- donor age >50 years;
- female sex;
- Cerebro-Vascular Accident (CVA)/ stroke as the cause of death;
- hypertension;
- diabetes mellitus;
- history of cocaine or methamphetamine use;
- high-inotrope requirement during donor management
- cardiac troponin;
- left-ventricular dysfunction;
- left-ventricular regional wall motion abnormalities, and;
- left-ventricular hypertrophy.

Time trends of allograft use and prevalence of donor risk factors were analyzed, to study the associations between donor risk factors and organ non-use. The primary outcomes examined were time-to-hospital discharge and recipient 30-day and 1-year survival. Their results are summarized in Table 2.2.

Only CVA as the donor cause of death marginally predicted prolonged recipient post-transplant hospitalization, and diabetes mellitus was the only donor predictor of increased recipient mortality. These findings concur with previous studies demonstrating the relatively small contribution of donor characteristics to post-transplant adverse events.

2.5 Predictors of Donor Heart Utilization for Transplantation in United States

Trivedi et al. [7] developed an objective system based on donor factors to predict donor heart use for Heart Transplantation (HTx). The multivariate logistic regression model uses various donor factors such as age, ejection fraction, creatinine, sex, bilirubin and troponin to predict the factors associated with the use of donor hearts for transplantation. Their results are summarized in Table 2.3.

Table 2.2: Unadjusted Odds Ratios for Associations Between Donor Risk Factors and Recipient Post-Transplant Outcomes

Donor Characteristics	30-d Mortality	*p*-value	1-y Mortality	*p*-value
Age>50y	1.97 (0.78-4.96)	0.150	1.23 (0.64-2.36)	0.540
Sex (female)	1.28 (0.59-2.79)	0.527	1.07 (0.66-1.74)	0.783
Cause of Death (CVA/Stroke)	1.17 (0.54-2.53)	0.699	1.02 (0.63-1.64)	0.950
Hypertension	1.42 (0.53-3.81)	0.488	0.76 (0.37-1.56)	0.449
Diabetes mellitus	6.35 (2.00-20.13)	0.002	3.07 (1.17-8.07)	0.023
Cocaine use	0.91 (0.40-2.09)	0.825	0.85 (0.51-1.40)	0.513
Peak dopamine dose >10 μg/kg per minute	0.79 (0.24-2.66)	0.707	0.82 (0.40-1.69)	0.586
Troponin I >1.0 μg/L	0.68 (0.27-1.71)	0.414	0.63 (0.36-1.11)	0.109
Left-ventricular hypertrophy	2.23 (1.02-4.86)	0.044	0.96 (0.56-1.65)	0.884
Left-ventricular ejection fraction <50%	1.41 (0.32-6.17)	0.647	0.60 (0.18-2.00)	0.409
Regional wall motion abnormalities	1.02 (0.35-3.00)	0.967	1.36 (0.75-2.47)	0.318

Table 2.3: Multivariate Logistic Regression Model to Identify Factors Associated with Donor Heart Use

Donor Variable.	Odds.
Troponin	0.998 (0.997, 1.000)
Age	0.945 (0.943, 0.948)
Body Mass Index (BMI)	1.020 (1.014, 1.026)
ejection fraction	1.096 (1.092, 1.100)
Bilirubin	1.001 (0.975, 1.027)
creatinine	0.927 (0.906, 0.949)
Diabetes 0 versus 1	2.190 (1.898, 2.527)
Liver used for transplantation 0 versus 1	0.508 (0.450, 0.574)
Sex, female versus male	0.674 (0.629, 0.723)
History of Cocaine No versus Yes	1.280 (1.172, 1.398)
Medical History no versus yes	2.527 (1.673, 3.819)
Brain death, stroke versus tumor no versus yes	0.616 (0.404, 0.939)
Brain death, anoxia versus tumor	0.602 (0.396, 0.917)
Brain death, head trauma versus tumor	1.296 (0.851, 1.974)
Cardiopulmonary resuscitation (CPR)	0.970 (0.857, 1.097)
Inotropic agents	1.627 (1.245, 2.126)

CHAPTER 3: METHODS AND DATA

3.1 Method

Two logistic regression models using donor characteristics that impact discard decision were built. Troponin data was not available for patients until 2005; it has been omitted in the regression model. The date at which an organ was recovered for transplantation distinguished the models from each other. The first model, derived from organ donors between (1995–2005) was used as an objective to decide whether or not to discard an organ in the second decade of study. The second model was cross-validated on the same population to decide: discard or not. The resulting transplantable organs from the two models were used in the organ allocation and acceptance simulation (i.e., TSAM).

R scripts were used to build the regression models and for cross-validation [28].

3.2 Study Population

3.2.1 Organ Donors

The participants of the study were registered heart donors on the UNOS deceased donor database whose organ recovery date was between 1995–2015. Currently the OPTN/SRTR donor dataset is divided into eight cohorts depending on the discard disposition shown in Table 3.1.

Table 3.1: Existing OPTN/STAR Cohorts

Heart Disposition Code	Reasons
.	Not reported
1	Authorization not requested
2	Authorization not obtained
3	Organ not recovered
4	Recovered not for Transplantation (Tx)
5	Recovered for Tx but not Transplanted
6	Transplanted
7	N/A
other	Unknown

The problem with the above classification is that it does not accurately represent the reasons for discard. Hence, we cleaned the data based on the disposition text into a more suitable representative cohorts. The donor organ dataset was therefore classified into 12 new categories, which are tabulated with counts in Table 3.2.

Table 3.2: Donor Organs: Cohorts

Cohort	Count (1995–2005)	Count (2005–2015)
Discarded due to Age	3310	2880
Discarded due to Cardiac arrest*	404	2834
Discarded due to Cardiac disease*	3640	6523
Discarded due to distance	1573	3831
Excl all disposition*	19518	27471
Discarded due to hepatitis	1085	1684
Discarded due to medical history*	2594	5512
Discarded due to no-consent*	2990	3857
Discarded due to poor organ quality*	404	1158
Discarded due to social history	320	479
Transplanted	22666	23606
Discarded due to other unknown reasons	998	188

*Hearts discarded due to cardiac arrest, cardiac diseases, medical history, no-consent from the donor's family, and poor organ quality were not included in the study. Hearts discarded due to above reasons would mean that they are not viable to be transplanted. Donor hearts which did not have the consent of the donor's family are always not recovered regardless of other factors.

The cohorts included for the study were all the hearts that were actually transplanted, marginal quality hearts, and hearts discarded when no suitable recipient were found locally. More specifically, they are classified as:

- Hearts discarded due to the age of the donor.
- Hearts discarded due to donor social history.

  Hearts discarded due to donor age and donor social history are considered ECD: These hearts however could have been used for transplantation if a recipient on the wait-list accepts it.
- Distance of the recipient: Hearts discarded because of the recipient's distance from the OPO were also used in the model. The current limitations in the cold storage system makes it difficult to transport donor heart to a patient far from the OPO. This leads to hearts viable for transplantation to be discarded.
- Hearts discarded due to hepatitis: Hearts that are hepatitis-positive were also included as there are no significant differences in patient survival and graft functions between hepatitis-positive and hepatitis-negative hearts transplanted [29].
- Other unknown (or undocumented) reasons.
- All transplanted hearts.

The population was divided into two model groups, based on the organ recovery date. The first model group contained all viable cohorts with organ recovery date between 01-01-1995 to 12-31-2005 (N=29,952) and the second model group contained viable cohorts with organ recovery date between 01-01-2005 to 12-31-2015 (N=32,668).

3.2.2 Patient/Recipient Wait-list

The recipient wait-list contained all patients waiting for an organ transplantation from 01-01-2009 to 12-31-2011. The wait-list was converted into a standard TSAM input file containing recipient's location, age, gender and medical history. This is later used to simulate the organ allocation process.

There is a certain significant difference in the number of patients on the waiting list with MCSD between the previous two decades of the study. A total of 6,220 patients had MCSD assisted support while on the waiting list registered from 2005–2015 whereas, a mere 218 patients were on MCSD support between 1995–2005.

3.3 Logistic Regression Models

Donor characteristics believed to impact discard decision of a heart were used to fit two logistic regression models. Model 1 is the regression model fitted from the 1995–2005 donor data and Model 2 is the regression model fitted from 2005–2015 donor data. These model acts as an objective to decide whether to discard a heart or not and mimics the transition of donor characteristics affecting the discard decision between the two decades.

3.3.1 Logistic Regression Model 1

The logistic regression Model 1 is derived using training data from donors registered between 1995–2005, with a positive response of discarded versus not discarded. Model 1 is cross-validated on its training set (heart donors from 1995–2005) and then used as an objective to test discard or not on 2005–2015 heart donor data.

Table 3.3: Logistic Regression Model 1 (1995–2005)

Donor Variable	Coefficient (95% C.I.)	Odds (95% C.I.)
Intercept	-1.649 (-2.447, -0.825)	0.192 (0.086, 0.432)
Age	-0.043 (-0.046, -0.040)	0.957 (0.955, 0.960)
BMI	0.030 (0.025, 0.036)	1.031 (1.025, 1.037)
Ejection Fraction	0.034 (0.033, 0.036)	1.035 (1.033, 1.036)
Bilirubin	0.019 (0.001, 0.038)	1.019 (1.000, 1.038)
Creatinine*	0.011 (-0.010, 0.034)	1.011 (0.989, 1.034)
Diabetes	0.485 (0.323, 0.646)	1.625 (1.382, 1.910)
Liver used for transplantation	-0.738 (-0.831, -0.645)	0.478 (0.435, 0.524)
Sex, female versus male	0.289 (0.213, 0.365)	1.335 (1.237, 1.440)
History of Cocaine	1.636 (1.506, 1.766)	5.133 (4.508, 5.846)
Medical History*	-0.178 (-0.771, 0.356)	0.837 (0.477, 1.468)
Brain death, stroke versus tumor	-0.187 (-0.366, -0.004)	0.830 (0.693, 0.994)
Brain death, anoxia versus tumor	0.225 (0.026, 0.426)	1.252 (1.025, 1.529)
Brain death, head trauma versus tumor	-0.497 (-0.676, -0.316)	0.608 (0.508, 0.728)
CPR	0.784 (0.508, 1.052)	2.191 (1.670, 2.875)
Inotropic agents	1.005 (0.707, 1.294)	2.731 (2.037, 3.662)

*Creatinine levels and donor medical history are not statistically significant factors corresponding to discard a heart from the year 1995–2005

History of cocaine use was the major characteristics determining discard with an odds ratio of 5.133, indicating a heart from a donor with a history of cocaine use ($\hat{x}$=1) is 5.133 times more likely to be discarded than a heart from a donor with no history of cocaine use ($\hat{x}$=0). Gender female versus male has an odds ratio of 1.335, which says the odds of a heart from a female donor ($\hat{x}$=1) is 1.335 times more likely to be discarded than a heart from a male donor ($\hat{x}$=0). Liver use for transplantation has a counter-effect on discard, having an odds ratio of 0.478—that is, a heart from a donor whose liver was transplanted ($\hat{x}$=1) is less likely to be discarded than a heart from a donor whose liver was not transplanted ($\hat{x}$=0). The odds ratio for all the donor characteristics are tabulated in Table 3.3.

Model 1 when tested with the actual records of whether or not donor hearts were discarded in 1995–2005, had an accuracy of 87.05%. The confusion matrix is shown in Table 3.4. Model 1 with 1,166 true positive predictions and 24,400 true negative prediction indicates the number of correct predictions from Model 1 on its training data. Model 1 has a high number of false negatives: 3,346. This high number of false negative in both the models is because hearts from cohorts like: discarded due to age, distance, hepatitis and donor social history are considered to build the model but were actually discarded.

The confusion matrix in Table 3.5 contains the predictions of Model 1 along with the two errors for a cutoff threshold of 0.5. At this cutoff Model 1 cross-validated on its training data has a sensitivity of $\frac{1166}{1166+3346} = 0.258$ and specificity of $\frac{24400}{24400+456} = 0.982$. True positive rate is equal to the sensitivity and false positive rate is given by (1−specificity) which is 0.018.

Table 3.4: Confusion Matrix for Model 1 Tested on 1995–2005 Data

Prediction \ Actual	Discarded	Not discarded
Discarded	1166	456
Not discarded	3346	24400

Receiver Operating Characteristics (ROC) summarizes the overall performance of our classifier across all thresholds of prediction-cutoff, given by the area under the curve. The two errors (type 1 and type 2) are plotted along the axes for all possible cutoff thresholds. The performance of the classifier improves with the increase in the area under the ROC curve.

The default prediction for both the models is (y-default=discard). A logistic regression cutoff probability of 0.5 is used as a cutoff to predict discard or not, where predictions greater than 0.5 are classified as discarded and predictions less than 0.5 are classified as not to be discarded.

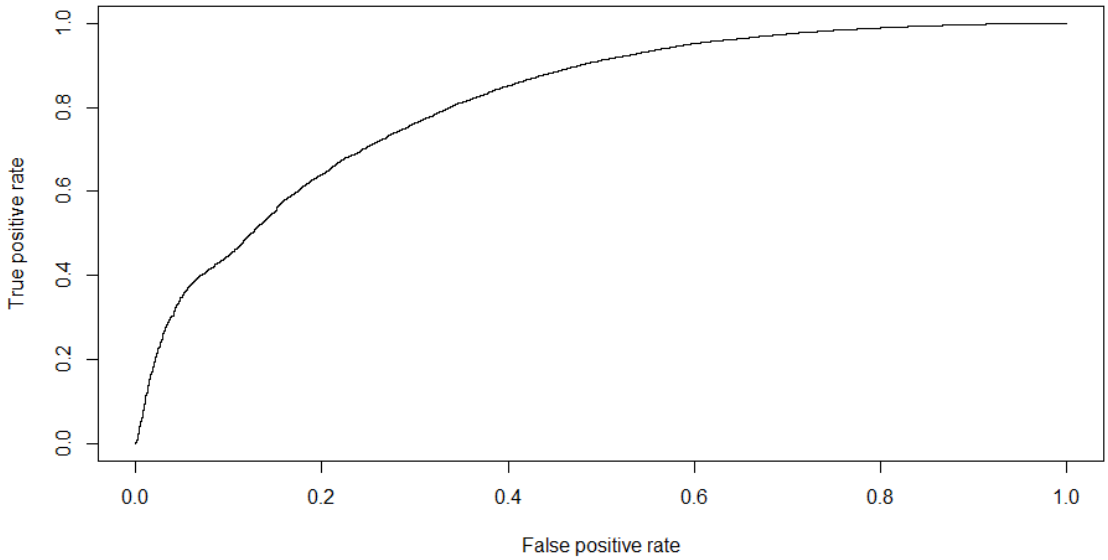


Figure 3.1: ROC Curve- Model 1 versus 1995–2005 Data

Model 1 was then used as an objective to decide whether or not an organ can be used for transplantation. All available donor hearts in the study from year 2005 to 2015 were tested for discards using this model.

Model 1 has 1,048 true positive predictions and 26,383 true negative predictions when tested on donor data for 2005–2015. At the same threshold for cutoff = 0.5, sensitivity is $\frac{1048}{1048+5887} = 0.151$ which is also the true positive rate and specificity of $\frac{26383}{26383+47} = 0.998$ (i.e., a false positive rate of 0.002).

It could be said that about 5,887 organs which met the quality standards of 1995–2005 were discarded. However, 47 hearts which were actually transplanted, was predicted to have been discarded by the model. In theory using Model 1 (quality standards followed from 1995–2005) would have resulted in 5,840 fewer discards in the decade 2005–2015 with an accuracy of 82.21%.

Table 3.5: Confusion Matrix for Model 1 Tested on 2005–2015 Data

Actual / Prediction	Discarded	Not discarded
Discarded	1048	47
Not discarded	5887	26383

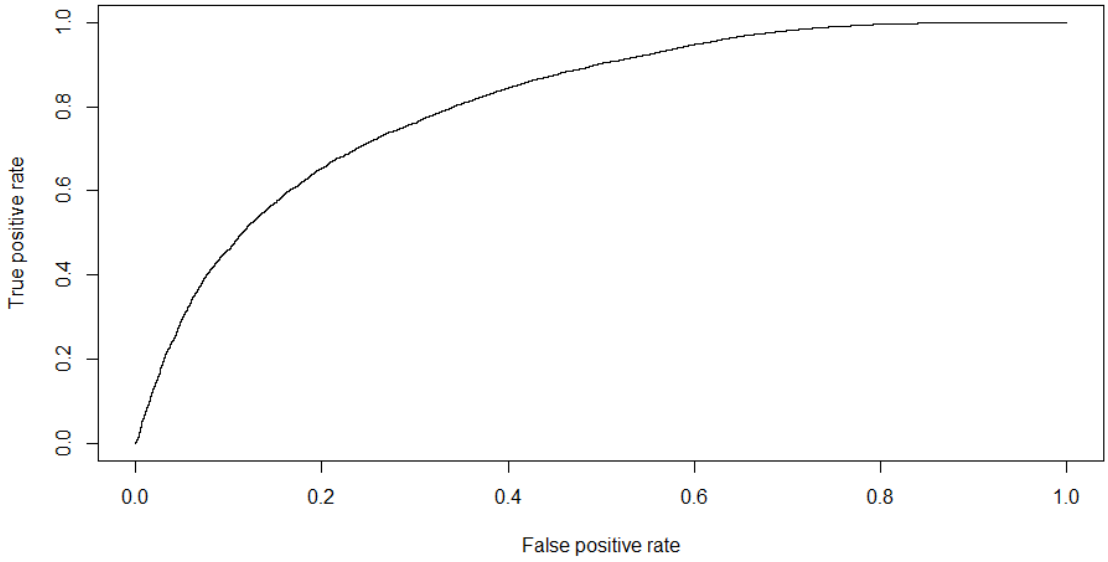


Figure 3.2: ROC Curve: Model 1 versus 2005–2015 Data

3.3.2 Logistic Regression Model 2

To study the changes in the effects of donor characteristics for discard between the two decades. Another logistic regression model using training data for 2005–2015 is built: Model 2. Model 2 is then used as an objective to test donor-heart discard in 2005–2015. Model 2 is compared with Model 1 to help understand the changes in donor organ characteristics of discarded hearts.

Table 3.6: Logistic Regression Model 2 (2005–2015)

Donor Variable	Coefficient (95% C.I.)	Odds (95% C.I.)
Intercept	-1.605 (-2.221, -0.987)	0.201 (0.108, 0.372)
Age	-0.059 (-0.061, -0.056)	0.943 (0.941, 0.946)
BMI	0.037 (0.0310, 0.042)	1.037(1.032, 1.043)
Ejection Fraction	0.053 (0.051, 0.055)	1.054 (1.052, 1.056)
Bilirubin*	0.014 (-0.007, 0.036)	1.014 (0.993, 1.036)
Creatinine	-0.028 (-0.052, -0.004)	0.972 (0.949, 0.996)
Diabetes	0.614 (0.487, 0.740)	1.848 (1.628, 2.097)
Liver used for transplantation	-0.570 (-0.676, -0.464)	0.565 (0.508, 0.629)
Sex, female versus male	0.487 (0.419, 0.555)	1.628 (1.520, 1.742)
History of Cocaine	0.682 (0.603, 0.760)	1.977 (1.829, 2.138)
Medical History*	0.332 (-0.029, 0.685)	1.393 (0.976, 1.989)
Brain death, stroke versus tumor	-0.316 (-0.490, -0.140)	0.729 (0.612, 0.868)
Brain death, anoxia versus tumor*	-0.005 (-0.180, 0.171)	0.995 (0.835, 1.185)
Brain death, head trauma versus tumor	-0.827 (-0.998, -0.652)	0.437 (0.368, 0.520)
CPR*	-0.004 (-0.137, 0.127)	0.996 (0.873, 1.136)
Inotropic agents*	0.135 (-0.137, 0.398)	1.145 (0.876, 1.495)

*Bilirubin levels, medical history, brain death by anoxia, CPR and inotropic agents are statistically not significant in determining discard. Compared to only medical history and creatinine levels being insignificant in Model 1.

The odds ratio for all the donor characteristics for Model 2 is shown in Table 3.6. The most significant factor associated with discarding a heart is donor history of cocaine use, with an odds ratio of 1.977. Indicating hearts from donors who have used cocaine is only 1.977 times more likely to be discarded, whereas the odds for cocaine use in the previous decade was 5.133. Followed by discard due to diabetic condition of the donor with an odds of 1.848 for a diabetic heart to be discarded. The odds for discard due to head trauma decreased to 0.437 from 0.608 in Model 1, this is because donors with brain death have been prioritized as preferred donors by the OPO. With research showing an improvement in donor heart quality with the use of suitable ventilators in brain dead donors [30].

The decreased odds for discard in Model 2 compared to Model 1, shows donor characteristic are becoming less important in deciding whether to discard a donor heart or not.

Model 2 (derived from the second decade, 2005–2015) when tested on heart donor data from 2005–2015 has an accuracy of 85.33%. Sensitivity of $\frac{2768}{2768+4167} = 0.399$ and a specificity of $\frac{25701}{25701+729} = 0.972$. The confusion matrix is given in Table 3.7. The high false positive prediction of 4,167 is due to using heart cohorts referenced in Table 3.2, which were actually discarded by the OPO when it could have been recovered.

Table 3.7: Confusion Matrix for Model 2 Tested on 2005–2015 Data

Prediction \ Actual	Discarded	Not discarded
Discarded	2768	729
Not discarded	4167	25701

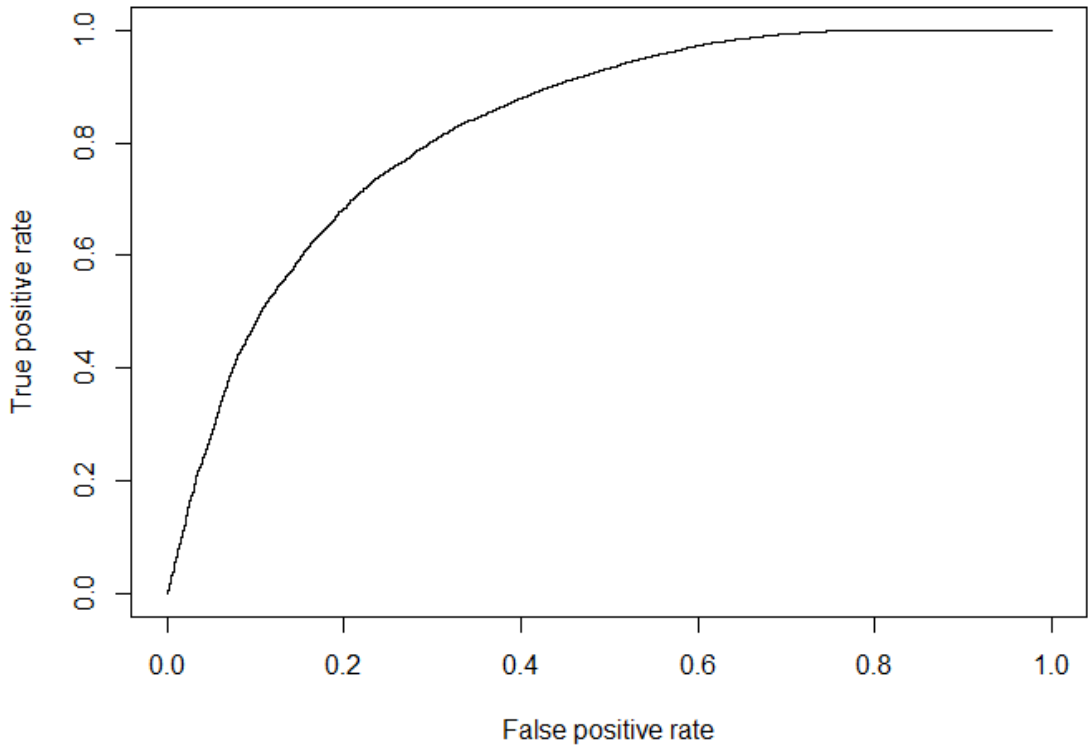


Figure 3.3: ROC Curve: Model 2 versus 2005–2015 Data

3.3.3 Utilization Rates Between Model 1 and Model 2

Utilization rate increased to 96.63% (Model 1) from 89.43% (Model 2), while the actual utilization rate for heart transplantation is 72.26%. This abnormal difference between the two models and the actual utilization rate could be caused by including cohorts discarded due to donor age, distance, etc. (shown in Table 3.2) in the models. Also, other reasons that results in discard decisions like heart not accepted by the recipient, no suitable recipient match, etc. are not captured in the regression models. To make sure Model 1 performs better than Model 2, organ allocation and acceptance is simulated using TSAM. This also tests if this increased utilization rate while using Model 1 also translates to increased transplant rate and decreased wait-list mortality rate.

Table 3.8: Comparision Between the Two Models and the Actual Discard Data

	Transplants	Discards	Utilization rate
Actual 05-15	23606	9062	72.26%
Model 95-05	32270	1005	96.63%
Model 05-15	26638	3150	89.43%

3.4 Organ Allocation and Acceptance Simulation Using TSAM

We use TSAM to evaluate how many of the hearts predicted by our models as viable for transplantation would have been accepted by a recipient on the wait-list. TSAM simulates organ arrival, allocation, and acceptance by the patient on the OPTN wait-list for 2009–2011.

Two sets of input data was created, which consisted of all hearts deemed to be transplantable by the two respective models between 07-01-2009 and 10-31-2011. The input files were transformed into standard TSAM formats. Current allocation policy of OPTN was used in the simulation. Each simulation was run 10 times with different random organ arrival events (i.e., arrival time of the donor heart).

3.5 Transplantation and Mortality Rates

The output of the TSAM contains summary of the number of transplants and deaths for each model according to the status and zone at the time of transplantation. To standardize the results we use transplantation and mortality rates. Transplant and mortality rates are normalized numbers of patients on the program wait-list who, respectively, undergo transplantation and die without transplantation for every 100 patient years on the wait-list.

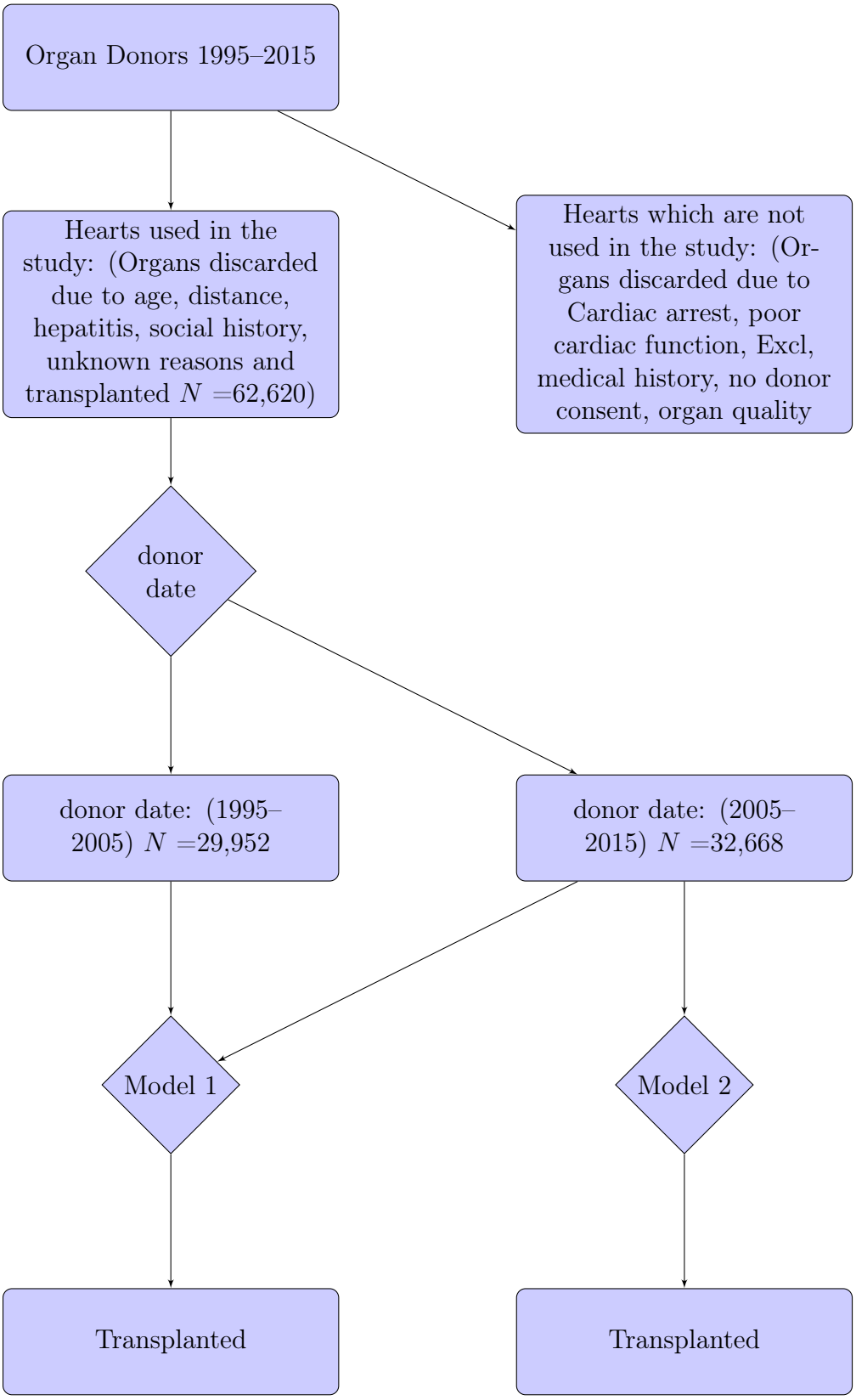


Figure 3.4: Both Predictor Models with Classification Cohorts

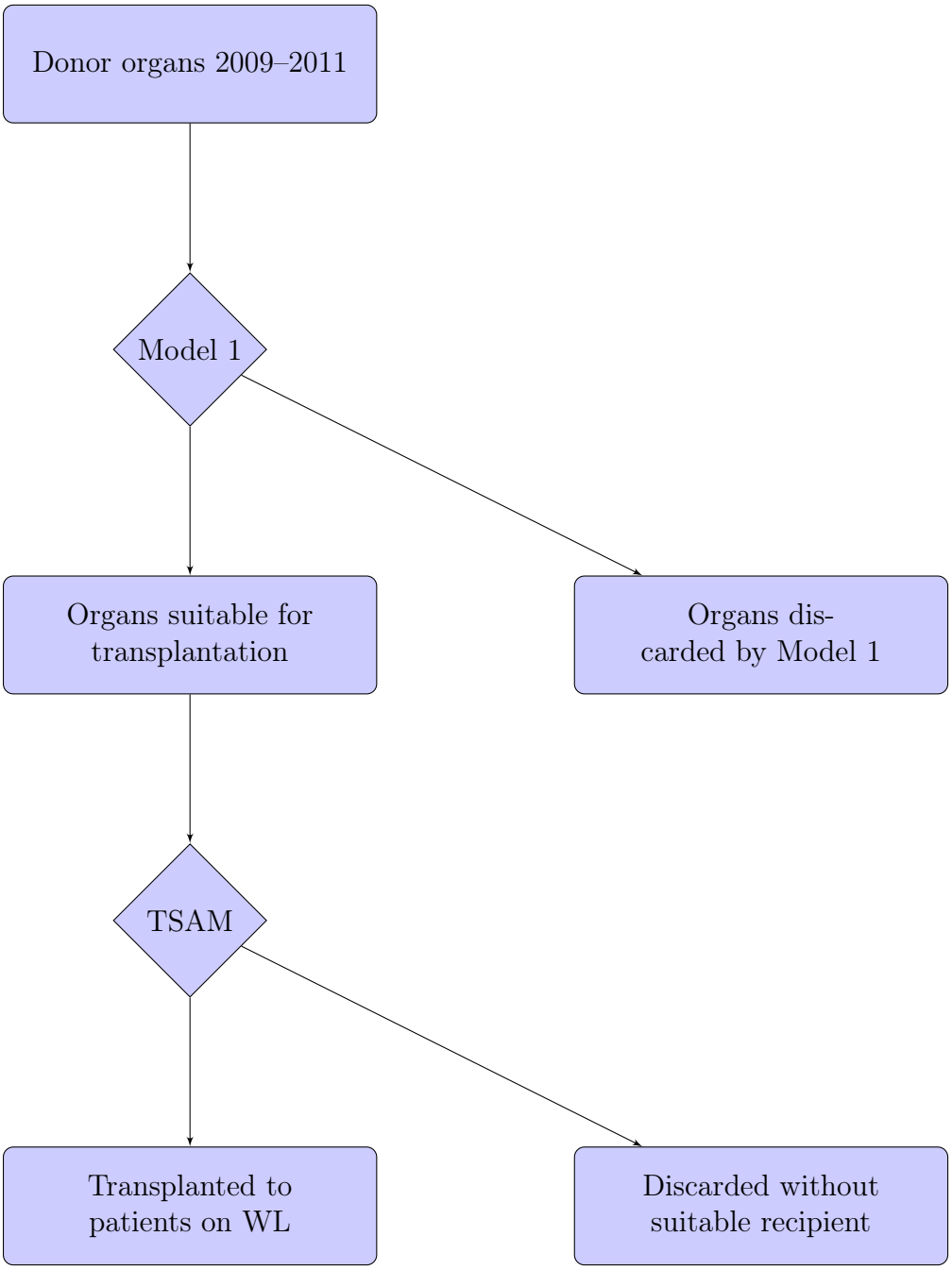


Figure 3.5: TSAM with 1995–2005 Predictor Model: Model 1

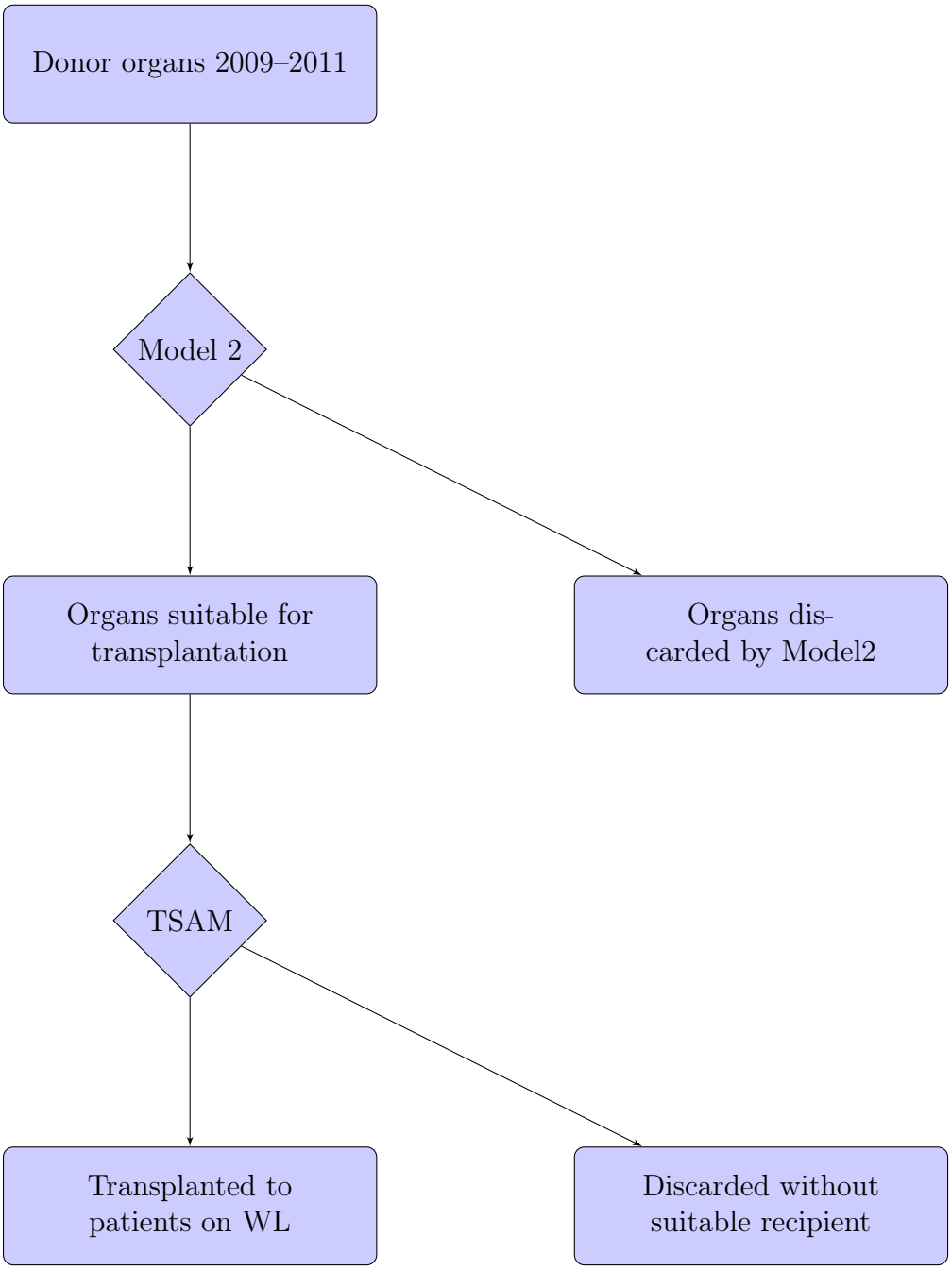
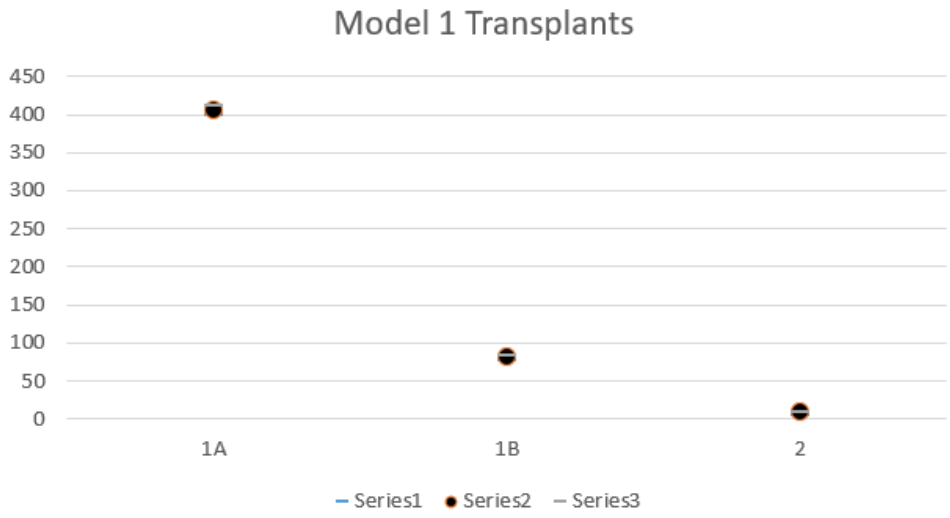


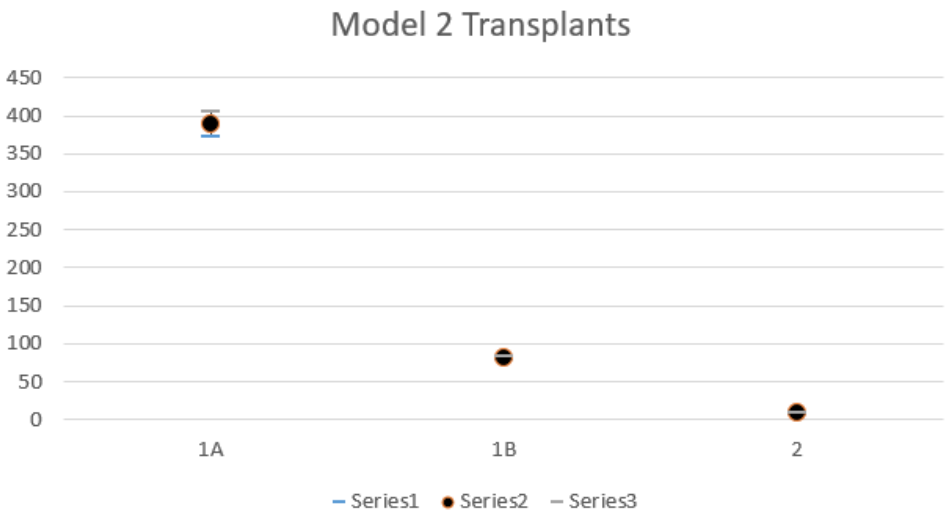
Figure 3.6: TSAM with 2005–2015 Predictor Model: Model 2

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Transplantation Rate



(a) Transplants per 100 patient years on the wait-list for Model 1 (1995–2005)



(b) Transplants per 100 patient years on the wait-list for Model 2 (2005–2015)

Figure 4.1: Transplants per 100 Patient Years on the Wait-list for both Logistic Regression Models

Table 4.1: Model 1 Transplant Rate

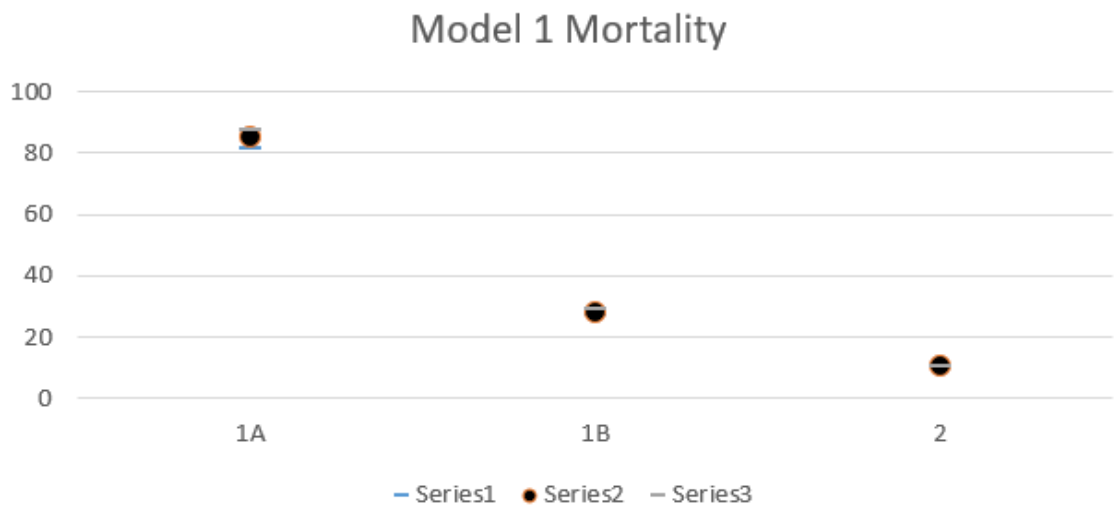
Status	Transplant Rates (95% C.I.)
1A	405.236 (404.182, 406.291)
1B	80.583 (80.209, 80.957)
2	8.214 (7.895, 8.533)

Table 4.2: Model 2 Transplant Rate

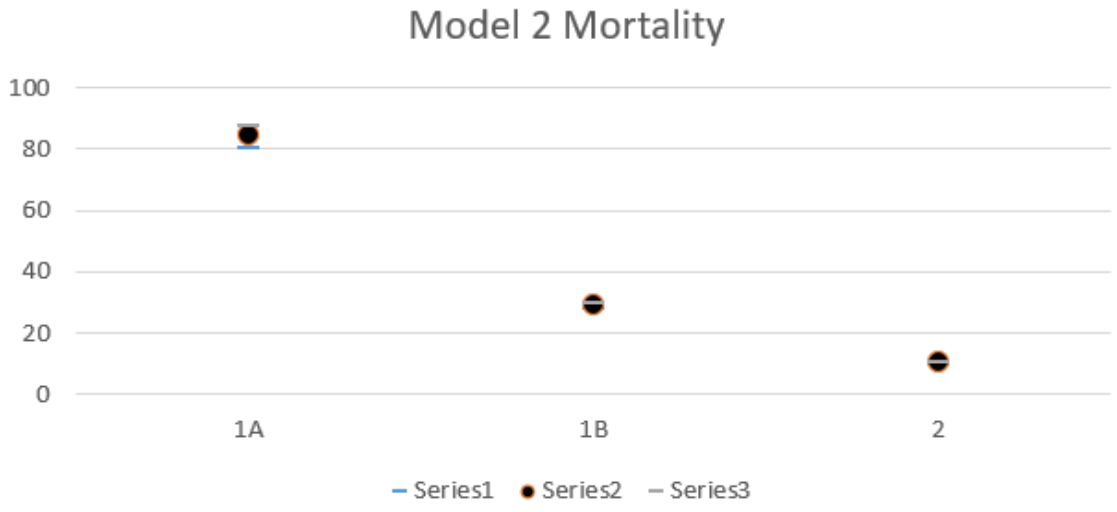
Status	Transplant Rates (95% C.I.)
1A	387.976 (386.038, 389.915)
1B	80.278 (79.899, 80.658)
2	8.106 (7.999, 8.213)

The transplant rate for Model 1 is significantly higher than transplant rate of Model 2 in the high priority status 1A. While there is no significant increase in the transplant rates between the two models in the lower priority Statuses 1B and 2.

4.2 Mortality Rate



(a) Mortality per 100 patient years on the wait-list for Model 1 (1995–2005)



(b) Mortality per 100 patient years on the wait-list for Model 2 (2005–2015)

Figure 4.2: Mortality per 100 Patient Years on the Wait-list for both Logistic Regression Models

Table 4.3: Model 1 Mortality Rate

Status	Mortality Rates (95% C.I.)
1A	84.854 (84.478, 85.230)
1B	28.054 (27.935, 28.173)
2	10.426 (10.397, 10.455)

Table 4.4: Model 2 Mortality Rate

Status	Mortality Rates (95% C.I.)
1A	84.667 (84.188, 85.146)
1B	28.891 (28.739, 29.042)
2	10.163 (10.116, 10.209)

The mortality rate in Status 1A is not significantly different between the two models. Status 1B mortality rate from Model 1 is significantly lesser than that of Model 2. In Status 2 however, Model 1 results in significantly larger mortality rate than Model 2, this should not undermine Model 1 because very few patients who are not critically ill remain in Status 2, and OPTN/SRTR allocation rules is designed to transplant more at higher priority statuses.

4.3 Discussion

UNOS allows patients bridged with MCSD to be placed in Status 1B and provides a 30-day grace period in Status 1A. In the event of device complications, these patients will be placed on Status 1A until they receive a transplant. This policy was adopted when MCSDs were unreliable. With advances in MCSD technology, patients bridged with mechanical support can survive longer than what was possible with older devices. This makes these patients selective while remaining in high priority statuses. Donor characteristics in Model 2 is not as significant in the discard decision as in Model 1.

This shows while the advancements in transplant therapy is allowing the use of hearts from donors with much worse medical condition than the previous decade, more hearts than before are being discarded.

The unchanged mortality rate between the two models in Status 1A shows that, even when the number of transplants decreased, the mortality rate did not change. This unchanged mortality in the high priority status can be associated with the reduced heart utilization rate despite the fact that the number of heart donors are increasing.

The increased transplant rate while using Model 1 supports the idea of using Model 1 as a predictive objective model to evaluate the decision to discard or not. This would allow OPOs to recover more hearts, and a corresponding allocation policy change can allow for these extra hearts to be offered to patients willing to accept them (i.e., not necessarily the patients in high priority statuses).

CHAPTER 5: CONCLUSION

The main aim of this study is to compare the two models, when it comes to the discard decision based on the donor characteristics. Model 1 had 5,840 fewer discards than Model 2. This difference, however, has little importance if a suitable recipient is not available to receive a transplant at that particular time. The transplant rates helps us better understand if there was a suitable recipient on the wait-list to receive these extra hearts. The increase in transplant rate of Model 1 over Model 2 shows that there were indeed patients who could have benefited from these additional hearts.

The better performance of Model 1 over Model 2 in both transplant rates and decreased mortality rates would mean that the hearts which could have been transplanted are being discarded. The unchanged mortality rate in Status 1A shows that the patients on high priority status will survive longer than before regardless of receiving a transplant early. Placing stable patients in the high priority statuses and the current limitations in transporting a donor heart over long distances has led to a decrease in heart utilization despite having donor heart shortages.

The study takes into account only donor characteristics as an objective model to decide whether an organ was discarded or not. But, other reasons like, no suitable recipient on the wait list and organ not accepted by the recipient when offered are also important in deciding whether or not to discard the organs.

Transplant rates and mortality rates are calculated based on the simulation model which starts from 07-01-2009 to 10-31-2011. The results even after normalizing for 100 patient years may not be accurate as the decision to accept or reject an offered heart depends on the recipient. TSAM only allows modeling accept/reject decision for the model run time only (which is a standard set by SRTR to evaluate policy

changes). So, it is difficult to find whether a patient who was offered a heart at a time different from the simulation run times accepts or rejects the heart.

Although MCSDs are believed to be one of the causes for the declining utilization rates, it is important to put critically ill patients on MCSD support, without which their chances of surviving on the wait-list reduces drastically. More research is needed to establish how patients bridged with MCSD are more selective than the patients who are not.

The policy of placing patients bridged with MCSD in high priority status has increased the wait times for patients with no MCSD support, this policy needs to be revisited to make sure MCSDs are used to improve patients' overall status and not merely used as a way to receive a transplant sooner.

Post-transplantation outcomes requires further evaluation, especially in the case of marginal quality hearts transplanted from Model 1 to make sure the outcomes are not different between the two models. If Model 1 outperforms Model 2 in post-transplantation survival outcomes it can be used as a predictive model for OPOs. This would provide OPOs a baseline to decide whether or not to recover a donor heart as opposed to making that decision based on the current trends in recovered donor heart characteristics.

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