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The Stanford experience of heart transplantation over five decades

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Aims Since 1968, heart transplantation has become the definitive treatment for patients with end-stage heart failure. We aimed to summarize our experience in heart transplantation at Stanford University since the first transplantation performed over 50 years ago.

Methods and results From 6 January 1968 to 30 November 2020, 2671 patients presented to Stanford University for heart transplantation, of which 1958 were adult heart transplantations. Descriptive analyses were performed for patients in 1968–95 ($n = 639$). Stabilized inverse probability weighting was applied to compare patients in 1996–2006 ($n = 356$) vs. 2007–19 ($n = 515$). Follow-up data were updated through 2020. The primary endpoint was all-cause mortality. Prior to weighting, recipients in 2007–19 vs. those in 1996–2006 were older and had heavier burden of chronic diseases. After the application of stabilized inverse probability weighting, the distance organ travelled increased from 84.2 ± 111.1 miles to 159.3 ± 169.9 miles from 1996–2006 to 2007–19. Total allograft ischaemia time also increased over time (199.6 ± 52.7 vs. 225.3 ± 50.0 min). Patients in 2007–19 showed superior survival than those in 1996–2006 with a median survival of 12.1 vs. 11.1 years.

Conclusion In this half-century retrospective descriptive study from one of the largest heart transplant programmes in the USA, long-term survival after heart transplantation has improved over time despite increased recipient and donor age, worsening comorbidities, increased technical complexity, and prolonged total allograft ischaemia time. Further investigation is warranted to delineate factors associated with the excellent outcomes observed in this study.

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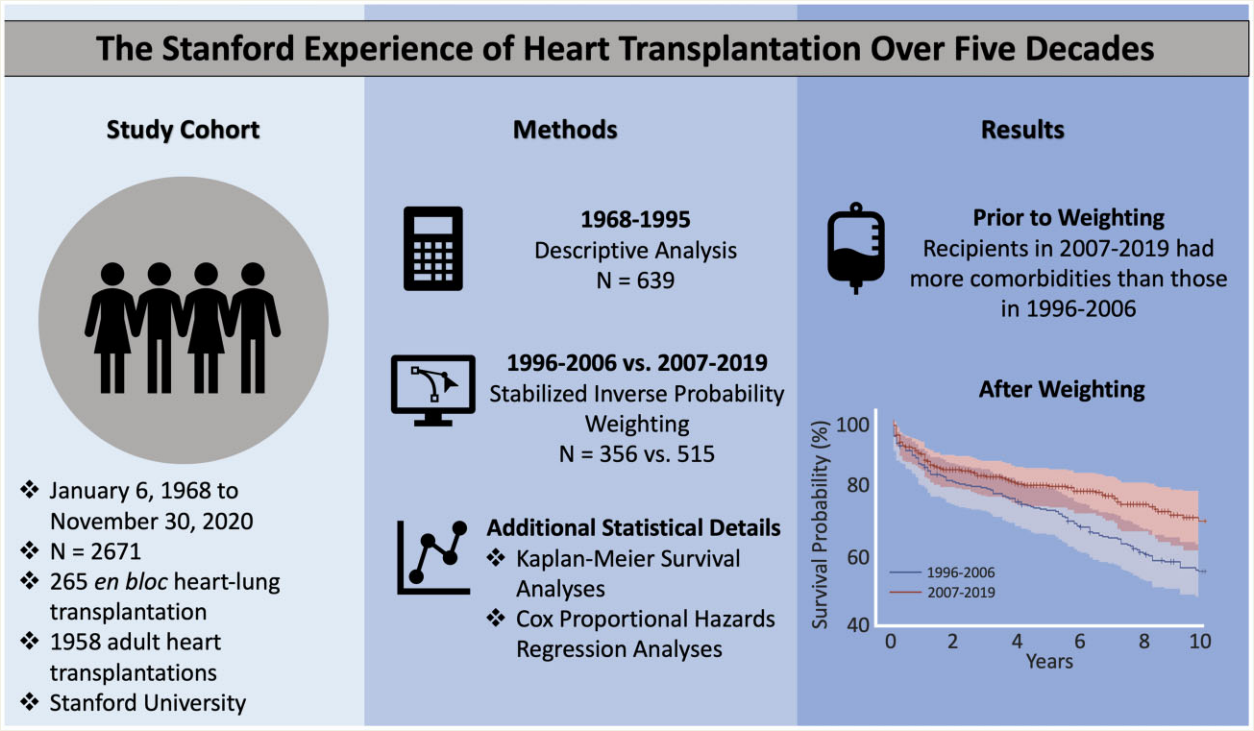
Graphical Abstract



Stanford experience of heart transplantation over five decades demonstrated improved long-term survival over time.

Keywords Heart transplantation • Outcomes • History

Introduction

Since the first adult heart transplantation in the USA on 6 January 1968 by Dr Norman Shumway at Stanford University, the procedure has gained worldwide acceptance.[1] Heart transplantation has become the definitive treatment for patients with end-stage heart failure. Although advancements in therapies have successfully delayed the progression to end-stage heart failure, the incidence and prevalence of heart failure continue to rise.[2] In 2019, heart transplantation was performed in 3552 patients in the USA compared to 3408 in 2018. The overall heart transplantation number continues to increase globally. With the development of mechanical circulatory support (MCS) technologies, these devices have been widely adopted since its inception.[3] Over the past few decades, advancements in immunosuppression, treatment of graft rejection, and surgical techniques have also likely led to improved survival after heart transplantation.[4] However, differences in patient characteristics, surgical details, and outcomes over the years remain unclear. The objective of this paper was to summarize and describe our experience in heart transplantation at Stanford University since the first transplantation performed over 50 years ago.

Methods

Patients

From 6 January 1968 to 30 November 2020, patients who received heart transplantations with and without other concomitant cardiac surgeries were identified in this study using the 9th or 10th revision of the International Classification of Diseases codes and Current Procedural Terminology codes. Historical departmental databases were also used to identify additional heart transplantation patients prior to the use of electronic medical records. A total of 2671 patients underwent heart transplantation at Stanford University. Of these, 265 were *en bloc* heart-lung transplantations, 448 were paediatric heart transplantations, and 1958 were adult heart transplantations. Retrospective chart review was performed using both paper and electronic medical records. Patients who underwent multiorgan transplantation or heart retransplantation were excluded. To allow for adequate follow-up for recent patients, 1510 adult patients who underwent isolated primary heart transplantation from 1968 to 2019 were included in the final cohort. Mortality is updated through 2020 using information obtained from the departmental historical databases, electronic medical record, and Social Security Death Index. The primary endpoint of this study was all-cause mortality, and secondary endpoints included postoperative outcomes. This study received approval from the Institutional Review Board at Stanford University, and the need for consent was waived.

Immunosuppression and antimicrobial prophylaxis

Our immunosuppression regimen has undergone several iterations. The initial regimen included azathioprine, prednisone, and horse anti-lymphocyte serum. In 1973, horse anti-lymphocyte serum was switched to rabbit anti-thymocyte globulin (RATG). In 1981, cyclosporine and prednisone became the mainstay of immunosuppression. In 2006, mycophenolate mofetil (MMF) replaced azathioprine, and tacrolimus replaced cyclosporine. Prednisone and RATG were continued. Our current immunosuppression regimen includes intraoperative methylprednisolone 500 mg IV, postoperative induction with RATG 1 mg/kg IV daily for three doses, tacrolimus with trough goal of 10–15 ng/mL for the first 6 months, MMF 1000 mg IV or PO twice daily, methylprednisolone 125 mg IV every 8 h for three doses, and prednisone 20 mg twice daily tapered over the first year.

Opportunistic infection prophylaxis regimens currently are trimethoprim and sulfamethoxazole for 1 year for *Pneumocystis jirovecii* prophylaxis, ganciclovir or valganciclovir for 6 months followed by acyclovir for 6 months for cytomegalovirus prophylaxis, itraconazole for 3 months, and nystatin until steroids are discontinued for fungal prophylaxis. Since 1993, aerosolized amphotericin has also been used postoperatively until discharge. Post-surgical prophylaxis includes cefazolin or vancomycin and piperacillin/tazobactam for 48 h.

Stabilized inverse probability weighting

Given the availability and reliability of prognostically important covariates, only patients who underwent heart transplantation from 1996 to 2006 ($n = 356$) were compared to patients from 2007 to 2019 ($n = 515$) for surgical details and outcomes. These two eras were chosen based on the use and volume of MCS and the change in immunosuppressive regimen to describe differences in two surgical epochs. Results for patients who underwent heart transplantation from 1968 to 1995 ($n = 639$) are presented in a descriptive manner.

From 1996 to 2019, patient baseline demographics and characteristics have changed. To ascertain the possible differences in outcomes if the same type of patients had undergone heart transplantation in 2007–19 as had undergone heart transplantation in 1996–2006, inverse probability weighting method was used to reduce casemix differences between the two time periods for descriptive analysis. To perform weighting, we first stratified patients based on preoperative MCS use status and whether a prior sternotomy had been performed. Preoperative MCS use was defined as MCS implantation such as ventricular assist device (VAD), intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), or Impella placement immediately prior to heart transplantation. Next, a non-parsimonious logistic regression model was used for those who underwent surgical repair from 1996 to 2006 vs. from 2007 to 2019 to balance the preoperative characteristics between the comparison groups to reduce differences in the casemix between the two periods. Variables used for propensity score (PS) calculation were age, gender, height, weight, and body mass index for both recipients and donors, recipient preoperative characteristics: hypertension, hyperlipidaemia, diabetes, coronary artery disease, dialysis, implantable cardioverter–defibrillator, and preoperative hospitalization, and recipient preoperative laboratory results of haemoglobin, platelet, creatinine, total bilirubin, aspartate transaminase, and alanine transaminase. Missing data for these variables were imputed with the average probability for each variable within the group. For each variable, a missing observation indicator was created. Stabilized inverse probability weighting (SIPW) was used to estimate the average treatment effect using the following equation: $\text{stabilizedweight} = \frac{Z\Pr(Z=1)}{PS} + \frac{(1-Z)\Pr(Z=0)}{1-PS}$, where Z represents time period ($Z = 1$ for 2007–19 and $Z = 0$ for 1996–2006), and $\Pr(Z = 1)$ and $\Pr(Z = 0)$ denote the marginal probability of the respective time period in the overall sample.[5,6] Inverse probability weighting also enabled the creation of a pseudo-population of patients in 2007–19 similar to the unweighted population of patients undergoing heart transplantation in 1996–2006 in terms of preoperative characteristics. This allowed us to minimize patient-level casemix differences of those undergoing heart transplantation during the two eras, therefore generating a reasonable assessment of differences in outcomes due to changes in clinical practice between the two eras. However, an increase in the variability of the estimated effect can result from a very large weight from a very low PS. SIPW therefore is an effective approach to solve this issue. Although the stabilization may add in small bias in the estimation of effects, it has the important benefit of reduced estimate variability. Finally, the standardized mean differences approach was used to assess the balance between the comparison groups, achieved by the weighting design. A standardized mean difference of <0.2 represents acceptable balance.[7]

Survival analysis

Kaplan–Meier survival analyses were performed on the weighted cohorts. Cox proportional hazards regression analyses were also performed to obtain the hazards ratio for overall mortality while adjusting for additional preoperative variables including preoperative VAD implantation, ventilator support, and history of cerebral vascular accident.

Surgical anastomosis analysis

Patients who underwent heart transplantation using the bicaval ($n = 446$) vs. biatrial anastomosis technique ($n = 35$) were identified for this subanalysis. Since the biatrial anastomosis technique was mostly used until 2012, the patient subgroup from 1996 to 2012 was used for this analysis. To compare outcomes after using the two anastomosis techniques, SIPW was performed using the same variables described above for PS calculation. Kaplan–Meier survival analyses were performed.

Additional statistical analyses and details

Continuous variables were analysed using *t*-test. Categorical variables were analysed using χ^2 test. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and comorbidities

There were 639 (40.9%) patients who underwent heart transplantation at Stanford University between 1968 and 1995. Average age of recipients at presentation for this historical cohort was 44.4 ± 11.4 years, and 98 (15.3%) were female. Average body mass index at presentation was 25.1 ± 4.6 kg/m^2. In terms of donor demographics, average age was 25.8 ± 8.9 years, and 25% were female. Donor average body mass index was 25.1 ± 4.7 kg/m^2.

For 1996–2006 vs. 2007–19, recipient and donor baseline demographics and comorbidities before and after weighting are shown in *Table 1*. Prior to weighting, recipients in 2007–19 compared to those in 1996–2006 were older (52.7 ± 12.8 vs. 51.2 ± 12.2 years) and had heavier burden of chronic diseases, such as hypertension (272/53.2% vs. 104/29.2%), hyperlipidaemia (241/47.1% vs. 74/20.8%), diabetes (191/37.4% vs. 73/20.5%), and chronic obstructive pulmonary disease (75/14.7% vs. 11/3.1%). More recipients in 2007–19 compared to 1996–2006 underwent preoperative VAD implantation (156/30.7%

Table 1 1996–2019 cohort before and after weighting

Variable	Before SIPW			After SIPW		
	1996–2006 ($n = 356$)	2007–19 ($n = 515$)	SMD	1996–2006 ($n = 337.4$)	2007–19 ($n = 484.9$)	SMD
Recipients						
Age (years)	51.2 ± 12.2 [54 (46, 60)]	52.7 ± 12.8 [56 (47, 62)]	-0.12	52.4 ± 10.4 [54 (48, 59)]	50.6 ± 14.2 [55 (43, 62)]	0.14
Female sex	76 (21.4)	142 (27.4)	0.05	70 (20.8)	124 (25.5)	0.11
Height (cm)	174.1 ± 10.8 [175.3 (167.6, 180.3)]	173.5 ± 9.9 [172.7 (167.6, 180.3)]	0.06	174.0 ± 9.9 [173.0 (169.0, 180.3)]	174.1 ± 9.6 [175.0 (167.6, 182.9)]	-0.01
Weight (kg)	79.3 ± 16.5 [78.5 (68.0, 89.8)]	80.5 ± 18.3 [78.9 (68.0, 92.1)]	-0.07	77.4 ± 15.3 [77.6 (63.5, 86.6)]	79.7 ± 17.3 [77.6 (68.0, 90.7)]	-0.14
BMI (kg/m^2)	26.1 ± 4.2 [25.4 (23.4, 28.4)]	26.6 ± 5.0 [25.9 (22.7, 30.0)]	0.09	25.5 ± 3.9 [25.2 (22.7, 27.4)]	26.2 ± 4.8 [25.3 (22.2, 29.3)]	-0.16
Race						
Caucasian	262 (73.6)	301 (58.5)		250 (74.0)	281 (57.9)	
African American	32 (9.0)	56 (10.9)		21 (6.2)	58 (12.0)	
Asian	21 (5.9)	68 (13.2)		17 (5.0)	64 (13.2)	
Hispanic	34 (9.6)	50 (9.7)		24 (7.2)	49 (10.1)	
Unknown	7 (1.9)	40 (7.7)		25 (7.6)	33 (6.8)	
Hypertension	104 (29.2)	272 (53.2)	-0.50	148 (43.8)	225 (46.7)	-0.06
Hyperlipidaemia	74 (20.8)	241 (47.1)	-0.58	126 (37.4)	180 (37.2)	0.01
Diabetes	73 (20.5)	191 (37.4)	-0.38	122 (36.1)	148 (30.7)	0.11
CAD	151 (42.4)	202 (39.5)	0.06	169 (50.0)	191 (39.6)	0.21
COPD	11 (3.1)	75 (14.7)	-0.42	10 (2.9)	73 (15.2)	-0.44
ICD	173 (49.7)	413 (81.9)	-0.72	208 (62.3)	337 (70.6)	-0.18
Prior sternotomy	49 (13.8)	207 (40.2)	-0.62	38 (11.2)	184 (37.9)	-0.65
Preoperative hospitalization	123 (34.6)	180 (35.4)	-0.02	99 (29.3)	166 (34.5)	-0.11
MCS	51 (14.3)	181 (35.2)	-0.50	41 (12.1)	159 (32.7)	-0.51
VAD	36 (10.1)	156 (30.7)	-0.53	35 (10.3)	142 (29.6)	-0.50
Ventilator support	26 (7.3)	73 (14.8)	-0.24	33 (9.9)	71 (15.2)	-0.16
WBC (k/μL)	8.3 ± 3.0 [7.9 (6.3, 9.9)]	8.1 ± 3.7 [7.3 (5.9, 9.4)]	0.07	7.8 ± 2.5 [6.9 (6.4, 8.9)]	8.3 ± 3.4 [7.6 (6.0, 10.0)]	-0.15
Haemoglobin (g/dL)	11.6 ± 2.0 [11.4 (10.1, 13)]	11.5 ± 2.2 [11.6 (10.0, 13.1)]	0.02	11.5 ± 2.0 [11.4 (9.9, 13.0)]	11.6 ± 2.2 [11.5 (9.9, 13.1)]	-0.05
Platelet (k/μL)	247.7 ± 108.0 [229.5 (181.5, 293.0)]	209.4 ± 71.5 [194.0 (159.5, 249.0)]	0.42	213.7 ± 89.3 [207.0 (151.0, 252.0)]	219.0 ± 71.4 [207.0 (165.0, 252.0)]	-0.06
Creatinine (mg/dL)	1.4 ± 0.5 [1.3 (1.0, 1.7)]	1.3 ± 0.4 [1.2 (1.0, 1.5)]	0.39	1.4 ± 0.5 [1.3 (1.0, 1.8)]	1.3 ± 0.4 [1.2 (1.0, 1.5)]	0.25
Total bilirubin (mg/dL)	1.3 ± 0.7 [1.2 (0.8, 1.8)]	1.0 ± 0.6 [0.8 (0.5, 1.2)]	0.53	1.3 ± 0.6 [1.1 (0.7, 1.6)]	1.2 ± 0.8 [0.9 (0.6, 1.7)]	0.12
AST (IU/L)	43.5 ± 30.2 [34 (25, 48)]	39.7 ± 28.9 [29.5 (23, 44)]	0.13	40.7 ± 23.0 [33 (24, 43)]	41.3 ± 29.6 [31 (24, 43)]	-0.02
ALT (IU/L)	41.7 ± 33.0 [31 (21, 45)]	45.1 ± 28.0 [38 (28, 51)]	-0.11	45.0 ± 30.9 [32 (22, 56)]	46.0 ± 27.9 [39 (29, 52)]	-0.03
Donors						
Age (years)	32.2 ± 12.2 [31 (21, 43)]	34.1 ± 12.6 [32 (23, 44)]	-0.15	35.9 ± 12.8 [37 (24, 46)]	34.0 ± 12.2 [33 (22, 43)]	0.16
Female sex	71 (19.9)	187 (32.0)	0.28	102 (30.4)	149 (27.3)	-0.07
Height (cm)	176.5 ± 9.3 [178.0 (170.0, 183.0)]	173.3 ± 9.4 [173.0 (167.0, 180)]	0.35	174.6 ± 9.3 [175.0 (165.0, 183.0)]	174.8 ± 9.4 [175.0 (169.0, 181.0)]	-0.03
Weight (kg)	82.0 ± 17.2 [80.0 (70.0, 90.0)]	79.5 ± 17.2 [77.0 (68.0, 89.0)]	0.15	80.5 ± 14.9 [79.0 (72.0, 87.0)]	80.6 ± 16.5 [77.2 (70.0, 90.0)]	-0.01
BMI (kg/m^2)	26.3 ± 5.0 [25.6 (22.6, 29.0)]	26.4 ± 5.0 [25.6 (22.7, 29.3)]	-0.02	26.5 ± 4.7 [25.7 (22.5, 29.0)]	26.4 ± 5.0 [25.6 (22.3, 29.2)]	0.02

Continued

Table 1 *Continued*

Variable	Before SIPW			After SIPW		
	1996–2006 ($n = 356$)	2007–19 ($n = 515$)	SMD	1996–2006 ($n = 337.4$)	2007–19 ($n = 484.9$)	SMD
Race						
Caucasian	216 (60.7)	253 (49.1)		220 (65.2)	250 (51.6)	
African American	29 (8.2)	38 (7.4)		23 (6.8)	37 (7.7)	
Asian	8 (2.3)	25 (4.9)		6 (1.8)	19 (4.0)	
Hispanic	88 (24.7)	138 (26.8)		79 (23.3)	132 (27.1)	
Unknown	15 (4.1)	61 (11.8)		9 (2.9)	47 (9.6)	
Hypertension	42 (11.9)	72 (16.2)	0.11	65 (19.6)	62 (14.3)	0.14
Diabetes	10 (2.8)	12 (2.5)	0.83	34 (10.2)	12 (2.7)	0.31
IV drug use	159 (45.4)	166 (52.7)	0.06	151 (45.3)	176 (53.5)	-0.16

Values are given as mean ± standard deviation [median (interquartile range)], or *n* (%).
Prior to weighting, recipients in 2007–19 were older and had heavier burden of chronic diseases than those in 1996–2006. Weighting adequately adjusted for most of the baseline differences in the variables used for weighting calculation and other patient characteristics.
ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CAD, coronary artery disease; CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter–defibrillator; IV, intravenous; MCS, mechanical circulatory support; SIPW, stabilized inverse probability weighting; SMD, standardized mean difference; VAD, ventricular assist device; WBC, white blood cell.

Table 2 Operative details after weighting

Variable	1996–2006, *n* = 337.4	2007–19, *n* = 484.9
Cross-clamp time (min)	103.1 ± 50.1 [91 (77, 104)]	101.9 ± 35.7 [96 (81, 114)]
Cardiopulmonary bypass time (min)	169.4 ± 79.6 [150 (120, 182)]	172.7 ± 48.9 [161 (137, 196)]
Warm allograft ischaemia time (min)	87.1 ± 58.8 [76 (76, 76)]	43.3 ± 11.1 [42 (35, 51)]
Total allograft ischaemia time (min)	199.6 ± 52.7 [204 (162, 228)]	225.3 ± 50.0 [228 (195, 258)]
Distance organ travelled (miles)	84.2 ± 111.1 [31 (19, 119)]	159.3 ± 169.9 [120 (25, 222)]

Values are given as mean ± standard deviation [median (interquartile range)].

Table 3 Postoperative outcomes after weighting

Variable	1996–2006 (*n* = 337.4)	2007–19 (*n* = 484.9)
Hospital length of stay (days)	19.4 ± 28.1 [13 (9, 25)]	20.7 ± 21.1 [14 (10, 21)]
Primary graft dysfunction	22 (6.4)	48 (10.0)
IABP	6 (2.4)	26 (5.7)
ECMO	5 (1.5)	16 (3.5)
MI	1 (0.3)	7 (1.5)
Temporary or permanent dialysis	33 (9.9)	71 (14.7)
Pneumonia	20 (6.1)	45 (9.4)
Urinary tract infection	17 (5.2)	17 (3.5)
Septicaemia	9 (2.8)	17 (3.6)
Rejection within 1 year requiring hospitalization	45 (13.3)	55 (11.4)
Number of rejections within a year	2.3 ± 1.4 [2 (1, 3)]	2.2 ± 1.7 [2 (1, 3)]

Values are given as mean ± standard deviation [median (interquartile range)], or *n* (%).
ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MI, myocardial infarction.

vs. 36/10.1%), required ventilator support (73/14.8% vs. 26/7.3%), and received MCS (181/35.2% vs. 51/14.3%). Average donor age also increased from 32.2 ± 12.2 years in 1996–2006 to 34.1 ± 12.6 years in 2007–19. Between 1996–2006 and 2007–19, there were no differences in donor hypertension (42/11.9% vs. 72/16.2%), diabetes (10/2.8% vs. 12/2.5%), or intravenous drug use (159/45.4% vs. 166/52.7%). All variables selected for PS calculation were appropriately balanced after the application of SIPW, except for recipient coronary artery disease and preoperative creatinine level (*Table 1*).

Operative details

A median sternotomy incision was routinely used. Organ donors were transferred to Stanford University for organ recovery until September 1973 when distant graft procurement was started. Implantation was performed according to the biatrial operative technique originally described in 1960, bicaval technique, or modern modified techniques.[8,16]

In 1968–95, average listed wait time was 195.6 ± 222.9 days. Distance organ travelled was 90.5 ± 110.8 miles. Average cardiopulmonary bypass time and total allograft ischaemia time were 110.4 ± 35.4 and 169.0 ± 46.3 min, respectively. The operative details from the weighted cohort from 1996–2006 to 2007–19 are shown in *Table 2*. Notably, the average listed wait time was decreased to 120.7 ± 229.7 and 122.9 ± 198.9 days in 1996–2006 and 2007–19, respectively. Distance organ travelled increased over time from 84.2 ± 111.1 to 159.3 ± 169.9 miles from 1996–2006 to 2007–19. Consequently, total allograft ischaemia time also increased over time (199.6 ± 52.7 vs. 225.3 ± 50.0 min). In contrast, warm allograft ischaemia time decreased from 1996–2006 vs. 2007–19 (87.1 ± 58.8 vs. 43.3 ± 11.1 min). Cross-clamp time and cardiopulmonary bypass time were similar between the two time periods.

Postoperative outcomes

For the historical cohort from 1968 to 1995, average hospital length of stay was 17.1 ± 1.6 days. The 30-day and 1-year mortality rates were 6.4% and 25.4%, respectively. Postoperative outcomes from the weighted cohort in 1996–2006 and 2007–19 are shown in *Table 3*. MCS was more commonly used in the perioperative period in 2007–19 compared to 1996–2006. More patients in 2007–19 received IABP (26/5.7% vs. 6/2.4%) and ECMO (16/3.5% vs. 5/1.5%) placement compared to those in 1996–2006. The use of temporary or permanent dialysis postoperatively increased from 9.9% to 14.7% from 1996–2006 to 2007–19. The incidences of severe postoperative rejection requiring hospitalization within the first year were similar between 1996–2006 and 2007–19 (45/13.3% vs. 55/11.4%), and the average number of severe rejection episodes was 2.3 ± 1.4 vs. 2.2 ± 1.7. There was no difference in hospital length of stay, primary graft dysfunction, myocardial infarction, or infection

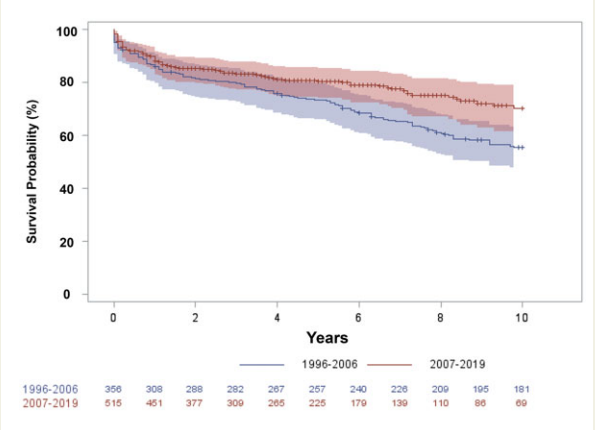


Figure 1 Kaplan–Meier survival analysis before the application of stabilized inverse probability weighting comparing patients who underwent heart transplantation in 1996–2006 vs. 2007–19. Patients who underwent heart transplantation in 2007–19 demonstrated superior survival compared to those who underwent heart transplantation in 1996–2006. Shaded area = 95% confidence interval. + = censored.

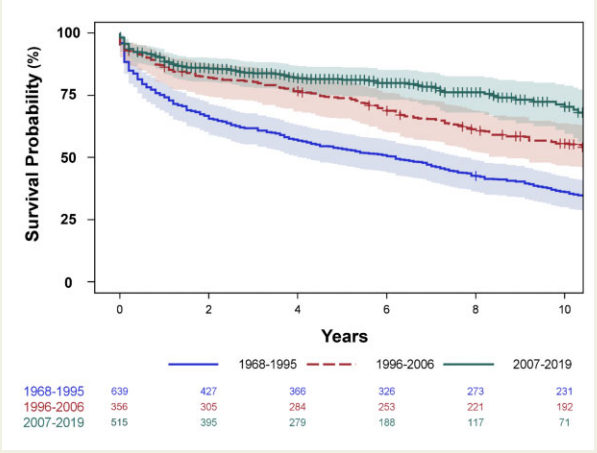


Figure 2 Overall unweighted Kaplan–Meier survival analysis comparing patients who underwent heart transplantation in 1968–95, 1996–2006, and 2007–19. Patients who underwent heart transplantation in 2007–19 demonstrated the most superior survival compared to those who underwent heart transplantation in 1996–2006 and 1968–95. Shaded area = 95% confidence interval. + = censored.

between the two periods. Lastly, in both 1996–2006 and 2007–19, the most common postoperative infection was pneumonia (20/6.1% vs. 45/9.4%), followed by urinary tract infection (17/5.2% vs. 17/3.5%) and septicaemia (9/2.8% vs. 17/3.6%). Postoperative infections were most commonly bacterial in 1996–2006 vs. 2007–19 (46/13.6% vs. 89/18.4%). Fungal (17/3.5% vs. 27/8.0%) and viral infections (12/2.4% vs. 33/9.9%) were decreased in 2007–19 compared to 1996–2006.

Survival

Prior to the application of SIPW, the average lengths of follow-up for patients undergoing heart transplantation in 1996–2006 vs. 2007–19 were 10.0 ± 6.6 vs. 4.8 ± 3.6 years. Patients in 2007–19 demonstrated improved survival compared to those in 1996–2006 (*Figure 1*). Improved survival was also observed when the historical patients were included from 1968 to 1995 (*Figure 2*). After the application of SIPW, the weighted 30-day and 1-year mortality rates were 11.0% vs. 3.1% and 18.8% vs. 10.4% for those in 1996–2006 vs. 2007–19. Patients in 2007–19 continued to show superior survival than those in 1996–2006 with a median survival of 12.1 vs. 11.1 years, respectively (*Figure 3*). Furthermore, patients who underwent heart transplantation in 2007–19 compared to those in 1996–2006 demonstrated persistent superior 30-day and 1-year survival (Supplementary material online, *Figure S1*). Conditional 1-year survival analysis of patients who survived at least 1 year after heart transplantation after the application of SIPW no longer demonstrated survival advantage in patients who underwent heart transplantation in 2007–19 over those in 1996–2006 (Supplementary material online, *Figure S2*). From 1996–2006, the leading cause of death for 1-year mortality was infection (47.1%/16) followed by graft failure (32.4%/11), other non-cardiac causes (17.6%/6), and malignancy (2.9%/1), whereas in 2007–19, graft failure (54.2%/26) was the primary cause of death at 1 year, followed by other non-cardiac causes (37.5%/18), infection (4.2%/2), and

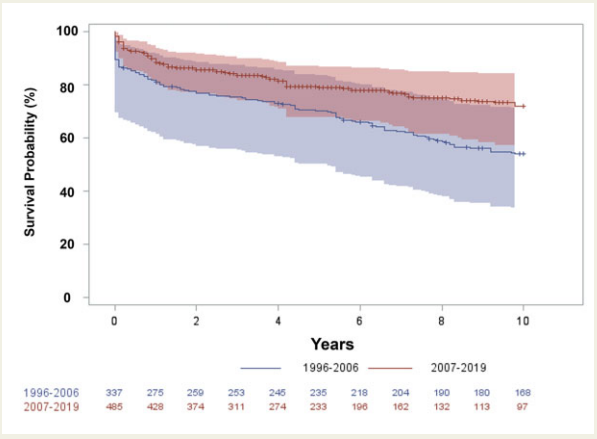


Figure 3 Kaplan–Meier survival analysis after the application of stabilized inverse probability weighting comparing patients who underwent heart transplantation in 1996–2006 vs. 2007–19. Patients who underwent heart transplantation in 2007–19 demonstrated superior survival compared to those who underwent heart transplantation in 1996–2006. Shaded area = 95% confidence interval. + = censored.

malignancy (4.2%/2). The causes of death for 5-year mortality were graft failure (43.1%/22), infection (35.3%/18), other non-cardiac causes (19.6%/10), and malignancy (2.0%/1) from 1996 to 2006, and graft failure (59.5%/47), other non-cardiac causes (32.9%/26), infection (5.1%/4), and malignancy (2.5%/2) from 2007 to 2019.

To adjust for additional preoperative factors that may impact survival outcomes, Cox proportional hazards regression analyses were

performed using the SIPW weighted cohort from 1996 to 2019. In 1996–2006 vs. 2007–19, the hazard ratio for 1-year mortality was 3.1 (95% confidence interval of 2.0 and 4.8), and the hazard ratio for overall mortality was 1.5 (95% confidence interval of 1.1 and 1.9). Preoperative ventilator support was another independent risk factor for 1-year mortality (hazard ratio 2.5, 95% confidence interval of 1.2 and 5.0) and overall mortality (hazard ratio 1.8, 95% confidence interval of 1.1 and 3.0).

Surgical anastomosis

Prior to the application of SIPW, there was no survival difference in patients who received heart transplantation using the bicaval vs. biatrial anastomosis technique (Supplementary material online, *Figure S3*). After SIPW, all variables used for weight calculation were appropriately balanced, except for recipient height, preoperative platelet count, and total bilirubin (Supplementary material online, *Table S1*). There was no difference in cross-clamp time (97.3 ± 29.5 vs. 97.9 ± 36.2 min), cardiopulmonary bypass time (158.3 ± 42.5 vs. 193.4 ± 98.5 min), or total allograft ischaemia time (218.1 ± 52.0 vs. 200.2 ± 51.7 min) using the bicaval vs. biatrial anastomosis technique. In terms of postoperative outcomes, between bicaval vs. biatrial anastomosis, there was no difference in hospital length of stay (18.0 ± 20.4 vs. 22.7 ± 27.5 days), primary graft dysfunction (23/5.1% vs. 1/3%), severe bleeding or cardiac tamponade requiring reoperation (18/4.1% vs. 1/2.7%), pacemaker implantation (25/5.6% vs. 3/8.3%), infection such as pneumonia (36/8.0% vs. 2/5.0%), urinary tract infection (11/2.5% vs. 2/5.2%), and septicaemia (12/2.7% vs. 1/3.8%), or severe rejection within the first year requiring hospitalization (41/9.1% vs. 5/13.3%). Four patients (1.2%) in the bicaval anastomosis group compared to 0 patients in the biatrial anastomosis group required tricuspid valve intervention for severe tricuspid regurgitation (TR) postoperatively. The weighted 30-day and 1-year mortality rates after using bicaval vs. biatrial anastomosis were 4.0% vs. 4.2% and 13.7% vs. 9.7%, respectively. The overall survival of heart transplantation patients using the bicaval vs. biatrial anastomosis technique was similar (Supplementary material online, *Figure S4*).

Discussion

In this half-century retrospective study from one of the largest heart transplant programmes in the USA, long-term survival after heart transplantation has improved over time (*Graphical abstract*). This is in accordance with the global trend in heart transplantation outcomes.[4,9,10] We hypothesize that this outcome improvement was likely associated with multiple factors. As surgeons gain more experience with heart transplantation, the improved donor management could have a positive impact on heart transplant recipient outcomes.[11] Additionally, with increased experience in organ procurement, we continued to improve donor allograft preservation methodology in an effort to reduce total allograft ischaemic time.[12,13] Early postoperative outcomes also greatly benefitted from short-term MCS use.[14] Finally, long-term allograft surveillance and management with advanced immunosuppression regimen has continued to improve over time.

In this study, we observed that in addition to an increase in technical complexity, recipient and donor age as well as comorbidities also increased over the decades. This creates one of the main challenges in making meaningful comparisons for patients undergoing heart transplantation during different eras. Given the patient composition changes over time, the SIPW methodology allowed us to effectively account for the changes to compare patients with similar observed preoperative characteristics during different time periods. Furthermore, total allograft ischaemia time increased. We believe that this was associated with an increase in organ distance travelled, which was likely due to the geographic location of our institution. Located in Northern California with only a few large transplant centres in the west coast, we regularly accept organs from a very broad range of geographic locations, as reflected by the wide range and high average distance organs travelled.[15] Despite these changes, our heart transplantation outcomes continued to improve. Interestingly, the survival advantage observed in recent years was primarily due to the improved short-term outcomes within the first year after heart transplantation. Preoperative ventilator support was a consistent risk factor for overall and 1-year mortality. We hypothesize that patients who were intubated preoperatively had heavier burden of chronic diseases and likely also require advanced support using MCS.

Since our programme's inception in 1968, our annual number of heart transplantations has continued to rise (Supplementary material online, Figure S5, S6). In 2020, 86 adult isolated heart transplantations were performed. With our increasing experience in cardiac transplantation, we adopted modified techniques to reduce total allograft ischaemia time and warm ischaemia time in select patients.[16,17] As demonstrated in this article, even though the total allograft ischaemia time increased over time, the warm allograft ischaemia time was reduced by half in recent years. We believe that this decrease in warm allograft ischaemia time may also play an important role in the improved outcomes observed in this study, as a previous study showed exacerbated acute rejection in lung allografts with prolonged warm ischaemia time.[18] Although it is known that increased total allograft ischaemia time was associated with worsened outcomes,[19] the exact relationship between warm allograft ischaemia time and postoperative outcomes warrants further analysis.

In addition to using modified techniques to reduce allograft ischaemia time, we have developed strategies to expand our recipient eligibility criteria and consider marginal donors.[20–26] This was associated with excellent outcomes, even in highly complex cases. With the advancement of allograft preservation techniques such as the TransMedics warm perfusion organ care system[13] and Paragonix SherpaPak cold transport system, we are actively exploring the avenues to further expand our donor pool by harvesting allografts across half of the country.

MCS, such as IABP, ECMO, and VAD, has evolved into a bridge to transplant or destination therapy, and the global use of MCS has increased dramatically since 2007.[4,27] At Stanford, MCS use continues to grow in both pre- and post-operative settings as shown in this study. Since October 2018, the new organ allocation system has placed higher priority for patients who require short-term MCS support rather than those who have received durable VADs. We anticipate that the number of MCS use as bridge to transplant will continue to increase. Specifically, left VAD has been shown to be associated with improved pulmonary vascular resistance.[28] Select patients who were initially considered not suitable for isolated heart

transplantation may be reconsidered again if their pulmonary vascular resistance improves after being on left VAD support. For patients who require pre-transplant ECMO support for left ventricular unloading, they can be weaned off of ECMO by using low dose inotropes, and then transitioned to IABP and potentially Impella. The left ventricular apex can also be cannulated to further unload the ventricle to prevent pulmonary oedema related to left ventricular dilation.

In this study, we stratified the cohort by preoperative MCS use but did not include individual MCS into the regression model for PS calculation, because it has been shown that the use of MCS as bridge to transplant was not associated with worse survival compared to that after direct primary transplantation.[4,9,10,29] There was also no difference in mortality on pump support compared with post-transplant mortality among those bridged from ECMO to VAD or heart transplantation based on the United Network for Organ Sharing database.[30] In another study, ECMO use was found to be associated with improved survival to discharge or transfer.[14] The preoperative MCS provided to the recipients is another reflection of clinical practice change over time as the technologies have gained wider adoption with evidence supporting the safety and benefits of preoperative MCS. The recent decade was associated with increased use of postoperative ECMO support, reflecting changes in postoperative patient management strategy over time. Our threshold for considering patients for ECMO support has decreased as short-term MCS technology continues to mature. Given our growing experience in ECMO, we believe that it is safer to place patients with severe primary graft dysfunction on ECMO support rather than relying on high dose inotropes and vasopressors. Similarly, we have a low threshold to initiate continuous renal replacement therapy in the early postoperative period to protect patients from acute kidney injury, volume overload-related right ventricular failure, and the associated sequalae.

The immunosuppression and antimicrobial prophylaxis regimens have undergone significant changes over time. Before the RATG was introduced in 1973, average hospital length of stay after transplantation was 69 days, and 10–15% of recipients would experience rejection within the first year of transplantation.[31] After the RATG was in use, hospital length of stay decreased by almost half.[31] In the past, patients who had severe rejections would receive solumedrol and RATG with or without intravenous immunoglobulin (IVIg), rituximab, or bortezomib treatment. Most recently, eculizumab and tocilizumab were introduced, but specific anti-rejection regimen varies depending on grading, type, and clinical symptoms. In December 1980, cyclosporine was introduced with significant outcomes improvement.[31] However, renal toxicity was observed, and the dosage was decreased from 17 mg/kg. In 2006, tacrolimus replaced cyclosporine, and MMF replaced azathioprine.[32] Currently, we are revising our immunosuppressant regimen so that RATG induction may only be indicated for those who are highly sensitized, with poor renal function, or are young African American women, while the steroid regimen may be biopsy result-based, allowing faster tapering schedule.

Cardiac allograft vasculopathy (CAV) is one of the most common indications for re-transplantation.[33–35] CAV is typically treated with mTOR inhibitors, such as sirolimus or everolimus, and statins. Chronic rejection in the form of CAV is one of the major factors that affects long-term graft and patient survival after heart transplantation. Though many factors can affect the development of CAV, immunologic mechanisms play the predominant role in the chronic rejection process.[36] At our institution, heart retransplant recipients would receive the same steroid treatment and a course of induction therapy with RATG. Even though our overall heart transplantation volume continues to expand, our centre's heart retransplantation rate remained stable during the recent decade. This trend may be another reflection of the improvement in long-term management post-transplantation.

Although changes in immunosuppression regimen have been shown to be associated with improved outcomes, continued survival improvement in the recent decade independent of immunosuppression regimen changes suggests that other factors may also contribute significantly to this clinical observation. For example, our matching process has evolved greatly over time. Initially, crude cell-based cross matching analyses were performed by mixing donor lymphocytes or lymph nodes with recipients' serum. Our current methods introduced more than a decade ago are much more sophisticated and include human leucocyte antigen cross matching and pre-transplant panel reactive antibody analyses. Patients who were noted to be highly sensitized would undergo desensitization treatment with IVIg with or without plasmapheresis treatment. Our rejection rates were also noted to have dropped, along with improved overall outcomes. Better donor-recipient matching may be one of the key factors in outcomes improvement.

The incidence of post-transplantation TR decreased since the introduction of bicaval anastomosis implantation technique by Yacoub *et al.* in 1989.[37,38] This was thought to be related to the decreased right atrial pressure and preserved right atrial size associated with using the bicaval rather than the biatrial anastomosis technique.[39] Though the bicaval anastomosis technique was previously found to be associated with superior short-term outcomes, long-term survival was similar compared to using the biatrial anastomosis technique.[39] In this study, we attempted to evaluate the impact of the bicaval vs. biatrial anastomosis technique and did not find either anastomosis technique to negatively impact postoperative outcomes or the need for future reoperation for tricuspid valve dysfunction. However, given the small sample size for the biatrial anastomosis group, it was difficult to achieve perfect balance after SIPW. The low incidences of tricuspid reintervention after heart transplantation also made it difficult to draw any conclusions. Therefore, the inference must be carefully drawn, and a more comprehensive analysis is needed to fully investigate the treatment effect of each anastomosis technique.

Post-transplant TR was also thought to be associated with endomyocardial biopsy (EMB), which may cause flail leaflets.[40–42] At our centre, surveillance for rejection was performed using EMB.[43,44] Up until a decade ago, EMB was performed weekly for the first month, followed by monthly for the first 6 months, then every 2–3 months until 3 years, and lastly every 6 months until 5 years after transplantation. Nowadays, EMB is performed if clinically indicated. Technologies such as Allosure® and Allomap® are used about 3 months after transplantation for non-invasive surveillance. Most recently, cell-free DNA analysis showed evidence of detecting early graft injury after lung transplantation[45] and may be used alongside or even replace EMB in the future for monitoring clinical antibody-mediated allograft rejections.

This was a retrospective single-centre study. Although the generalizability of the results is uncertain, as a historical review of the natural history of heart transplantation at a high-volume centre with more granular data than what national and international registries can provide, this study offers extremely unique perspectives. The other limiting factor of this study was its incomplete data for patients prior to the adoption of the electronic medical record system. Significant effort has been made to retrieve data in all forms, but the limiting factor of incomplete data may be the nature of a large, retrospective study spanning over half a century. Lastly, even though several sub-analyses, such as the impact of preoperative short-term MCS on patient outcomes, would be interesting to conduct to further elucidate the differences observed in this study, they were not feasible to perform due to the low incidences.

In conclusion, in this half-century retrospective descriptive study from one of the largest and longest running heart transplant programmes in the USA, long-term survival after heart transplantation has improved over the decades, despite increased recipient and donor age, worsening comorbidities, increased technical complexity, and prolonged total allograft ischaemia time. Though this study does not attempt to pinpoint the causal mechanisms that led to the changes in outcomes, it does provide important insights into what has changed over time. Improved matching, sensitivity testing, and heart failure treatment along with the evolution of immunosuppression medications and MCS may have all contributed to the excellent outcomes observed in the modern era.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: none declared.

Data availability

The data underlying this article cannot be shared publicly due to patient privacy. The data will be shared on reasonable request to the corresponding author.

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