Long-term Survival After Heart Transplantation: A Population-based Nested Case-Control Study

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Background. Heart transplantation is the mainstay of treatment for patients in end-stage heart failure. This study sought to contrast survival after transplantation with that of the general population to quantify standardized mortality rates using a nested case-control study design.

Methods. Control subjects were noninstitutionalized inhabitants of the United States identified through the National Longitudinal Mortality study. Case subjects were adults who underwent heart transplantation between 1990 and 2007 and identified through the Organ Procurement and Transplantation Network. Propensity-matching (5:1, nearest neighbor, caliper = 0.1) was utilized to identify suitable control subjects based on age, sex, race, and state of permanent residency. The primary study endpoint was 10-year survival.

Results. In all, 31,883 heart transplant recipients were matched to 159,415 noninstitutionalized residents of the United States. The 10-year survival of heart transplant recipients was 53%. The population expected mortality rate was 15.9 deaths per 100 person-years with an observed rate of 45.1 deaths per 100 person-years (standardized mortality rate [SMR] 2.84; 95% confidence interval, 2.82 to 2.87). The broadest gaps between observed and expected survival were evident in female (SMR 3.63), black (SMR 3.67), and Hispanic (SMR 4.12) recipients. Standardized mortality ratios declined over time (1990 to 1995, 3.09; 1996 to 2000, 2.90; 2001 to 2007, 2.58). The long-term standardized survival of older recipients was closest to that expected for their age.

Conclusions. Heart transplant recipients have considerable long-term survival and have a threefold higher standardized long-term mortality rate than that of the noninstitutionalized population. Long-term mortality rates have consistently declined over time and will likely continue to decrease.

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Heart transplantation is the mainstay of treatment for end-stage heart failure and remains as the only intervention to provide extended survival for this prevalent disease.[1,2] Fortunately, this intervention has been around for 50 years, benefited the lives of more than a hundred thousand recipients, and has been the subject of extensive outcomes research.[3,4] Despite these unprecedented milestones, several questions remain. How does the life expectancy of heart transplant recipients compare with that of the general population? Are there subgroups of recipients who come closer to their population-expected survival? And if there is a gap in long-term survival, has it positively changed over time? This study attempts to respond these questions by examining the long-term survival of heart transplant recipients in the United States in reference to contemporaneous noninstitutionalized inhabitants.

Patients and Methods

The present study utilized a population based nested case-control design to quantify the standardized survival of heart transplant recipients compared with the noninstitutionalized population. For each case subject, five controls were identified by matching across age, sex, race, and state of residency. This study was approved by the Johns Hopkins Medicine Institutional Review Board, which waived the need for individual participant informed consent.

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Selection Criteria

Control subjects were adult inhabitants (aged 18 years or more) of the 48 contiguous states, the District of Columbia, or Alaska. The National Longitudinal Mortality Study (NLMS) provided the publicly available Public Use Microdata Sample files. The NLMS sought to study the effects of demographic and socioeconomic characteristics in US mortality rates. It was based on a sample of the noninstitutionalized inhabitants of the United States. The NLMS consists of US Census Bureau data from current population surveys and a subset of the 1980 Census combined with death certificate from the National Center for Health Statistics to identify time and cause of death. This study was conducted between the late 1980s and early 1990s. Every subject was followed for 11 years, providing a wide sample of the US population with enough longitudinal follow-up to examine survival.

Case subjects were adult patients (aged 18 years or more) who received transplants between January 1, 1990, and December 31, 2007, in either of the 48 contiguous states, the District of Columbia, or Alaska. This geographic selection was made to match the regions surveyed by the NLMS. Subjects who underwent multiple organ, repeat, or heterotopic heart transplantation were excluded from this analysis. The Organ Procurement and Transplantation Network provided the publicly available Standard Transplant Analysis and Research files. These files comprise a prospectively collected dataset of all thoracic organ transplantation in the United States since 1987. Patients underwent transplantation in 171 different centers, and follow-up was available until August 31, 2018.

Study Endpoints

The primary endpoints were observed survival and standardized mortality ratio (SMR) at 10 years. Ten years is a commonly examined endpoint that coincides with the 11 years encompassed by the NLMS. The 1990 to 2007 transplantation study period was selected to focus only on recipients who accrued at least 10 years of follow-up. Data collection procedures and variable definitions for both sources of data have been previously described.[5-7]

Statistical Analysis

A nested sample was selected from the population-based study sample using propensity matching. Having met specific conditions, a propensity score predicts the likelihood of being assigned to the treatment arm (in this case, receiving a heart transplant). A multivariable logistic regression model was developed using subject age, sex, race, and state of permanent residency. A propensity score was generated for each study subject using this regression model. Matching was performed in a 5:1 ratio of control to case subjects, using the nearest-neighbor principle, and caliper set to 0.1. Covariate balance was examined through the change in absolute standardized mean differences, which express the difference between two groups in standard deviations. Obtaining absolute differences less than 0.1 was used to confirm adequate covariate balance. Although propensity matching is traditionally utilized to risk-adjust to estimate independent treatment effects, this study utilized it merely as a tool to find a demographically similar control pool in the general population to generate unbiased standardized mortality rates.

The actuarial survival estimates of matched study subjects were generated using the Kaplan-Meier method. Conditional survival estimates were generated for study subjects that survived the first year. Unadjusted survival comparisons were made with the log rank test. Expected survival estimates and SMR were calculated in reference to matched controls. Ninety-five percent confidence intervals (CI) for standardized mortality ratios were generated based on exact values of the Poisson distribution.

Cause of death for each subject was categorized according to the standardized list published by the National Center for Health Statistics.[8] Competing outcomes analysis was used to examine causes of death. This analysis was performed to examine differences in survival between case and control subjects. Nonparametric estimates of cumulative incidence functions were generated for the following clusters of cause of death: cardiovascular, cerebrovascular, graft failure, infection, malignancy, pulmonary, and other. Differences between incidence functions were tested with the *K*-sample Anderson-Darling test.

Categoric variables are presented as count of patients (percentage) and continuous variables as mean ± SD. Statistical significance was defined by α less than 0.05 (two-sided). Analyses were performed using R version 3.5.2.[9]

Results

During the study period, 31,892 patients underwent heart transplantation in the United States and 31,883 (99.9%) were successfully matched for this analysis (Table 1). In the NLMS files, 1,334,341 noninstitutionalized adults were identified and 159,415 (11.9%) were successfully matched for this analysis (Figure 1). Before matching, 9 case subjects and 2412 subjects were excluded for missing values impeding complete case matching. The distribution of propensity scores among study subjects was consistent and homogeneous after matching (Supplemental Figure 1). Matching yielded adequately balanced samples, confirmed by every absolute standardized mean difference being less than 0.1 after matching (Supplemental Figure 2).

The 10-year survival of transplant recipients was 53% compared with 84% for matched control subjects (Figure 2). The absolute difference in actuarial survival estimates between study arms increased linearly over time (1 year, 13%; 3 years, 17%; 5 years, 21%; 10 years, 31%). Five-year survival was slightly higher for men (73% vs 70%, log rank $P < .001$); however, 10-year survival was similar for men and women (53% for both; Supplemental Figure 3). The absolute difference in actuarial survival was larger for women (1 year, 14%; 3 years,

Table 1. Demographic Characteristics of Study Subjects Before and After Matching

Demographics	Controls (n = 1,334,341)	Cases (n = 31,892)	Matched Controls (n = 159,415)	Matched Cases (n = 31,883)
Age, y[a]	42.3 ± 16.3	51.8 ± 11.5	51.6 ± 15.5	51.8 ± 11.5
Sex				
Male	632,632 (47.4)	24,746 (77.6)	125,599 (78.8)	24,740 (77.6)
Female	701,709 (52.6)	7146 (22.4)	33,816 (21.2)	7143 (22.4)
Race				
White	1,049,327 (78.6)	25,334 (79.4)	127,879 (80.2)	25,334 (79.5)
Black	117,010 (8.8)	4133 (13)	19,267 (12.1)	4133 (13)
Hispanic	119,808 (9)	1639 (5.1)	8324 (5.2)	1639 (5.1)
Other	45,784 (3.4)	777 (2.4)	3945 (2.5)	777 (2.4)
Missing	2412 (0.2)	9 (0)	0 (0)	0 (0)
State[b]				
AK	15,718 (1.2)	58 (0.2)	273 (0.2)	58 (0.2)
AL	18,074 (1.4)	305 (1)	1600 (1)	305 (1)
AR	16,611 (1.2)	311 (1)	1732 (1.1)	311 (1)
AZ	18,344 (1.4)	557 (1.7)	2656 (1.7)	557 (1.7)
CA	112,019 (8.4)	3341 (10.5)	16,268 (10.2)	3339 (10.5)
CO	19,588 (1.5)	345 (1.1)	1856 (1.2)	345 (1.1)
CT	14,190 (1.1)	394 (1.2)	2052 (1.3)	394 (1.2)
DC	11,821 (0.9)	38 (0.1)	194 (0.1)	38 (0.1)
DE	12,767 (1)	112 (0.4)	542 (0.3)	112 (0.4)
FL	54,217 (4.1)	1802 (5.7)	8839 (5.5)	1801 (5.6)
GA	20,731 (1.6)	667 (2.1)	3282 (2.1)	667 (2.1)
HI	13,319 (1)	54 (0.2)	294 (0.2)	54 (0.2)
IA	18,946 (1.4)	308 (1)	1640 (1)	308 (1)
ID	17,226 (1.3)	136 (0.4)	660 (0.4)	136 (0.4)
IL	52,285 (3.9)	1259 (3.9)	6716 (4.2)	1259 (3.9)
IN	21,095 (1.6)	838 (2.6)	3978 (2.5)	838 (2.6)
KS	17,851 (1.3)	327 (1)	1828 (1.1)	327 (1)
KY	17,658 (1.3)	600 (1.9)	3018 (1.9)	600 (1.9)
LA	16,351 (1.2)	777 (2.4)	3357 (2.1)	777 (2.4)
MA	37,138 (2.8)	501 (1.6)	2467 (1.5)	501 (1.6)
MD	20,741 (1.6)	534 (1.7)	2904 (1.8)	534 (1.7)
ME	15,128 (1.1)	97 (0.3)	438 (0.3)	97 (0.3)
MI	47,200 (3.5)	897 (2.8)	4800 (3)	897 (2.8)
MN	20,122 (1.5)	523 (1.6)	2759 (1.7)	523 (1.6)
MO	23,282 (1.7)	697 (2.2)	3633 (2.3)	696 (2.2)
MS	17,664 (1.3)	368 (1.2)	1913 (1.2)	368 (1.2)
MT	17,644 (1.3)	62 (0.2)	348 (0.2)	62 (0.2)

(*Continued*)

Table 1. Continued

Demographics	Controls (n = 1,334,341)	Cases (n = 31,892)	Matched Controls (n = 159,415)	Matched Cases (n = 31,883)
NC	36,020 (2.7)	1093 (3.4)	5673 (3.6)	1093 (3.4)
ND	17,766 (1.3)	62 (0.2)	325 (0.2)	62 (0.2)
NE	17,250 (1.3)	174 (0.5)	842 (0.5)	174 (0.5)
NH	12,786 (1)	88 (0.3)	417 (0.3)	88 (0.3)
NJ	41,776 (3.1)	1374 (4.3)	6798 (4.3)	1373 (4.3)
NM	20,222 (1.5)	151 (0.5)	724 (0.5)	150 (0.5)
NV	16,634 (1.2)	156 (0.5)	754 (0.5)	156 (0.5)
NY	81,994 (6.1)	1918 (6)	10,314 (6.5)	1917 (6)
OH	53,113 (4)	1355 (4.2)	7136 (4.5)	1355 (4.2)
OK	18,242 (1.4)	529 (1.7)	2791 (1.8)	529 (1.7
OR	16,920 (1.3)	316 (1)	1711 (1.1)	316 (1)
PA	54,480 (4.1)	1934 (6.1)	9653 (6.1)	1934 (6.1)
RI	13,222 (1)	91 (0.3)	437 (0.3)	91 (0.3)
SC	15,544 (1.2)	399 (1.3)	2125 (1.3)	399 (1.3)
SD	18,850 (1.4)	59 (0.2)	324 (0.2)	59 (0.2)
TN	17,012 (1.3)	677 (2.1)	3185 (2)	677 (2.1)
TX	69,452 (5.2)	2614 (8.2)	11,889 (7.5)	2614 (8.2)
UT	17,944 (1.3)	251 (0.8)	1339 (0.8)	251 (0.8)
VA	22,719 (1.7)	926 (2.9)	4338 (2.7)	925 (2.9)
VT	12,943 (1)	46 (0.1)	222 (0.1)	46 (0.1)
WA	18,417 (1.4)	572 (1.8)	2957 (1.9)	571 (1.8)
WI	21,878 (1.6)	948 (3)	4224 (2.6)	948 (3)
WV	17,183 (1.3)	206 (0.6)	952 (0.6)	206 (0.6)
WY	14,244 (1.1)	45 (0.1)	238 (0.1)	45 (0.1)

[a]Age is mean ± SD; [b]Standard US state abbreviations used.

Values are n (%).

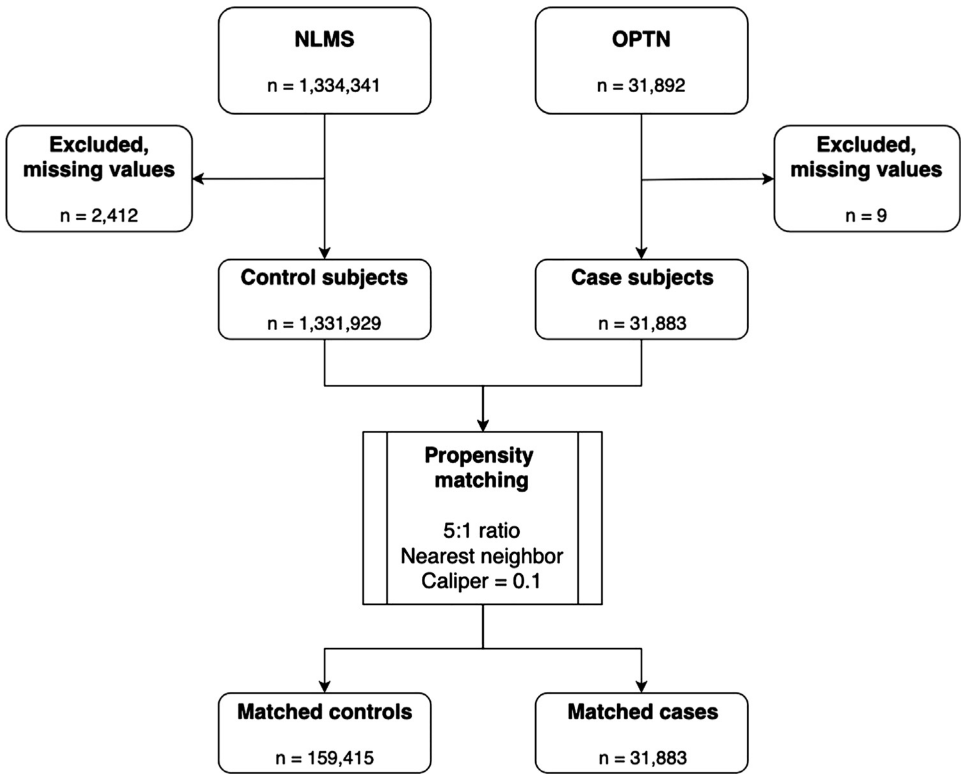

Figure 1. Flow diagram of patients in the study. Propensity matching was utilized to select a nested control population among noninstitutionalized inhabitants of the United States in the National Longitudinal Mortality Study (NLMS). (OPTN, Organ Procurement and Transplantation Network.)

19%; 5 years, 25%; 10 years, 35%) than men (1 year, 13%; 3 years, 16%; 5 years, 19%; 10 years, 30%) given that the survival estimates for female controls were higher. Ten-year survival after transplantation was higher for recipients who underwent transplantation in recent eras (1990 to 1995, 49%; 1996 to 2000, 53%; 2001 to 2007, 57%; Supplemental Figure 4). Supplemental Figure 5 illustrates survival estimates for recipients stratified by race.

Conditional survival estimates were generated to reexamine these data after filtering out the increased hazards of mortality of the early posttransplantation period. The 10-year conditional survival of transplant recipients was 62% compared with 85% for matched control subjects (Figure 3). The absolute difference in conditional survival estimates between study arms also increased linearly over time (3 years, 5%; 5 years,

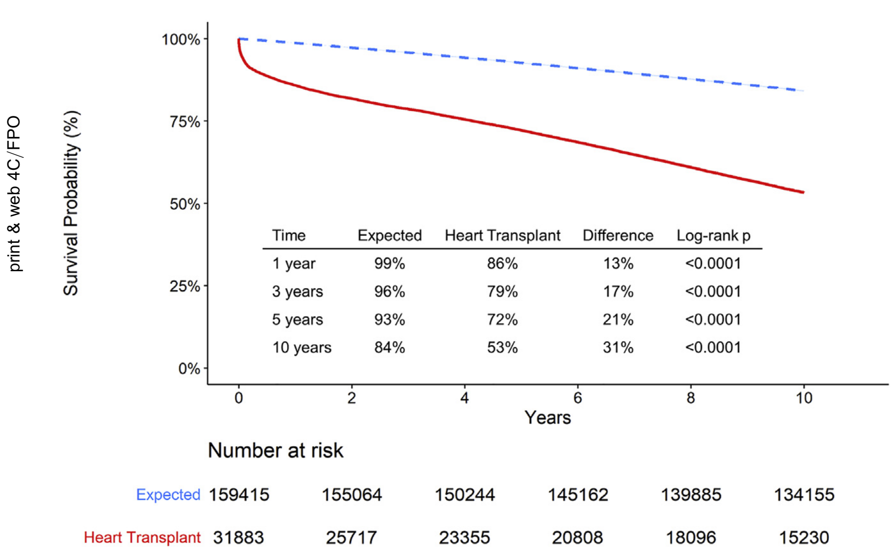

Figure 2. Ten-year actuarial survival after heart transplantation (red line). Expected survival estimates (blue line) were calculated from noninstitutionalized, propensity-matched, control subjects. Estimates generated with the Kaplan-Meier method with 95% confidence intervals. Differences in survival were tested with the log rank test.

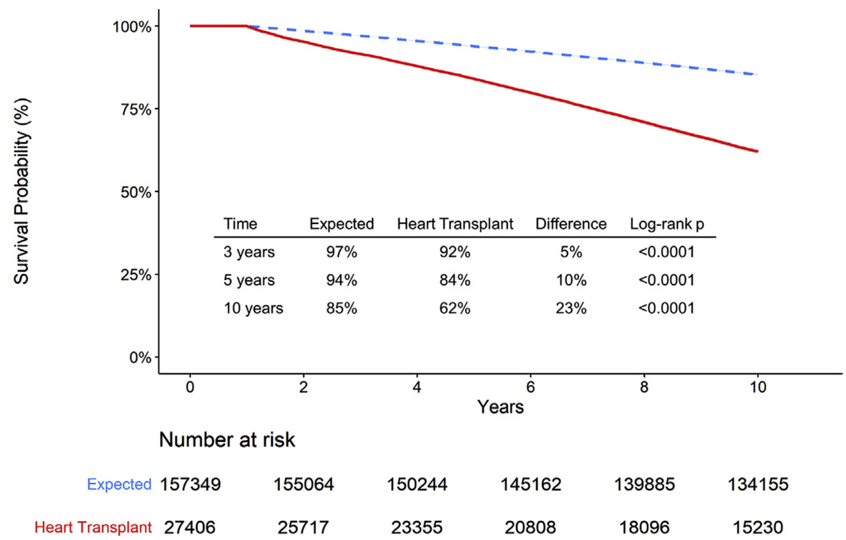

Figure 3. Ten-year survival conditional on survival to 1 year after heart transplantation (red line). Expected survival estimates (blue line) were calculated from noninstitutionalized, propensity-matched, control subjects. Estimates generated with the Kaplan-Meier method with 95% confidence intervals. Differences in survival were tested with the log rank test.

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10%; 10 years, 23%). Similar sex-related (Supplemental Figure 6), temporal (Supplemental Figure 7), and racial (Supplemental Figure 8) differences became evident in subgroup analysis for conditional survival.

The overall expected number of deaths among case subjects was 5055 with an expected mortality rate of 15.9 deaths per 100 person-years. Over the study period, 14,386 case subjects died with an observed mortality rate of 45.1 deaths per 100 person-years. The overall SMR was 2.84 (95% CI, 2.82 to 2.87; Figure 4, Supplemental Table 1). The SMR was higher for women (3.62; 95% CI, 3.57 to 3.69) than men (2.68; 95% CI, 2.66 to 2.71). White recipients had the lowest SMR (2.65; 95% CI, 2.62 to 2.68). Standardized mortality ratios decreased over time (1990 to 1995, 3.09; 1996 to 2000, 2.90; and 2001 to 2007, 2.58). Standardized mortality ratios decreased proportionally with increasing age, and patients less than 30 years of age had the highest ratios (18 to 24 years; 43.6; 25 to 29 years, 44.5; Figure 5, Supplemental Table 2). Recipients more than 60 years of age had the lowest SMR; however, these only correspond to a small fraction of the usual transplantation population. Recipients in Louisiana (SMR 4.54; 95% CI, 4.35 to 4.73), Texas (SMR 4.36; 95% CI, 4.25 to 4.47), Wisconsin (SMR 4.15; 95% CI, 3.97 to 4.34), Virginia (SMR 3.96; 95% CI, 3.79 to 4.14), and Nevada (SMR 3.93; 95% CI, 3.54 to 4.36) had the highest rates of mortality (Figure 6, Supplemental Table 3).

The cumulative incidence of death at 10 years from cardiovascular (8.6% vs 6%), cerebrovascular (1.7% vs 0.9%), graft failure (6.4% vs 0%), infection (6.7% vs 0.6%), malignancy (5.6% vs 4.5%), other (10.3% vs 2.6%), or pulmonary (1.8% vs 1%) causes were higher for transplant recipients than for matched controls (every *K*-sample $P < .001$). There was early separation between cumulative incidence curves between case and control subjects, apart from death from malignancy (Figure 7).

Comment

In the United States, more than half of heart transplant recipients are alive after 10 years. The mortality rate of transplant recipients is only threefold higher than in the noninstitutionalized population. Standardized mortality rates vary substantially across age, sex, and racial groups. Young, female, and Hispanic patients had high SMR due to the relatively higher expected survival among their controls. However, black patients also had a high standardized mortality without higher expected survival, unfortunately reflecting lower observed survival after transplantation. The standardized mortality of transplant recipients has decreased over time, which is likely due to advancements in medical therapy and donor-recipient matching.

This is the first examination of survival after heart transplantation in comparison with that of the regular population despite tens of thousands of performed transplants and decades of outcomes research. Heart transplantation has been called the only curative intervention for end-stage heart failure on several occasions.[10-12] These results do not substantiate such claims. Yet, heart transplantation stands as the single most beneficial intervention that modern medicine can offer to extend survival and return quality of life.[13] Unfortunately, the cumulative incidence of death from cardiovascular causes remains higher (10 years, 9%) than expected (10 years, 6%). One must take into consideration the additional incidence of death from graft failure at 10 years (observed, 6%), which is inextricably also death from a cardiovascular cause.

Although women represent 53% of the population captured by the NLMS, only 22% of heart transplant recipients were women. This discrepancy exists in the United States and other countries performing heart transplantation, with only 21% of recipients being female.[14] Size matching between donors and recipients is

	n	%	Observed	Expected	SMR
Sex					
Male	24,740	77.6	11,132	4,147	2.68
Female	7,143	22.4	3,236	892	3.63
Race					
White	25,334	79.5	11,155	4,211	2.65
Black	4,133	13.0	2,214	603	3.67
Hispanic	1,639	5.1	698	170	4.12
Other	777	2.4	301	68	4.44
Transplantation era					
1990-1995	10,497	32.9	5,145	1,664	3.09
1996-2000	9,337	29.3	4,295	1,480	2.90
2001-2007	12,049	37.8	4,928	1,910	2.58
Total	31,883	100	14,386	5,055	2.84

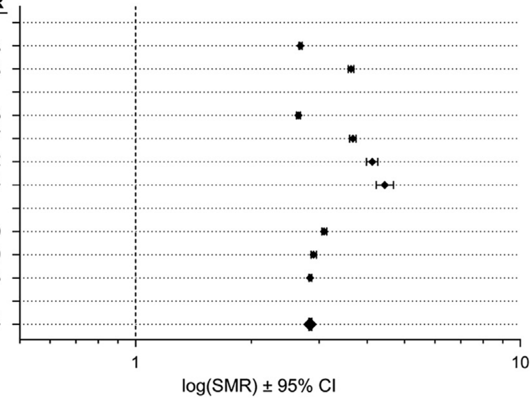

Figure 4. Number of recipients, observed and expected deaths, and standardized mortality ratio (SMR) with 95% confidence interval (CI) by recipient demographic characteristics. Expected number of deaths was calculated in a subset of control subjects with the same demographic characteristics. Logarithmic transformation (log) was used for the horizontal axis. Numeric values available in Supplemental Table 1.

routinely utilized by centers to select pairs within a 20% to 30% margin,[15] and female candidates may be at a theoretical matching disadvantage. However, the reason behind this discrepancy in proportion that exists in heart transplantation remains unclear.[16]

Young recipients, female recipients, and Hispanic recipients had the highest mortality rates compared with the general population. We believe these rates are high largely due to the control demographic to which these recipients are being compared. According to the Global Burden Disease Study, these demographic groups have the highest life expectancy in the United States.[17] This theory could potentially explain why SMR gradually decreases in indirect proportion to increasing age in Figure 5.

These findings should be interpreted keeping in mind that this study period is truncated at 2007, and the decreasing trend in standardized mortality may continue for patients receiving transplantation after this period. Several patterns have evolved in the field of heart transplantation since the end of this study. Donor shortage is the main limitation of heart transplantation and new avenues to expand the donor pool—such as ex vivo organ perfusion,[18] graft procurement after circulatory death,[19] and utilization of hepatitis C viremic donors[20,21]—are under constant investigation. Mechanical circulatory support has become the most common mode of support for candidates awaiting transplantation, and more than half of adult recipients are being bridged to transplantation with a ventricular assist device.[22] In addition, tacrolimus-based maintenance immunosuppression regimens—now utilized in more than 95% of recipients—are the mainstay of management, with fewer than half of recipients receiving them before 2008.[23,24] Predicting whether standardized 10-year mortality will continue to decrease in the face of these changes is challenging. However, 1-year and 5-year mortality rates have continued to decline and have historically correlated with long-term mortality rates.[23]

The adjusted cumulative incidence of causes of death for transplant recipients varied greatly with the general population. These results indicate that there is early

Age, years	n	%	Observed	Expected	SMR
18 - 24	1,151	3.6	512	12	43.6
25 - 29	814	2.6	388	9	44.5
30 - 34	1,105	3.5	422	17	24.8
35 - 39	1,575	4.9	671	42	16.2
40 - 44	2,391	7.5	955	91	10.5
45 - 49	3,795	11.9	1,535	230	6.68
50 - 54	5,544	17.4	2,327	507	4.59
55 - 59	6,811	21.4	3,127	998	3.13
60 - 64	5,804	18.2	2,892	1,248	2.32
65 - 70	2,568	8.1	1,349	788	1.71
70 - 78	325	1.0	190	148	1.28

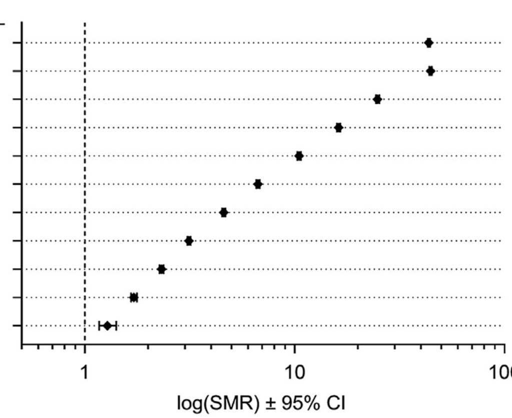

Figure 5. Number of recipients, observed and expected deaths, and standardized mortality ratio (SMR) with 95% confidence interval (CI) by recipient age groups. Expected number of deaths was calculated in subset of control subjects with the same age range. Logarithmic transformation (log) was used for the horizontal axis. Numeric values available in Supplemental Table 2.

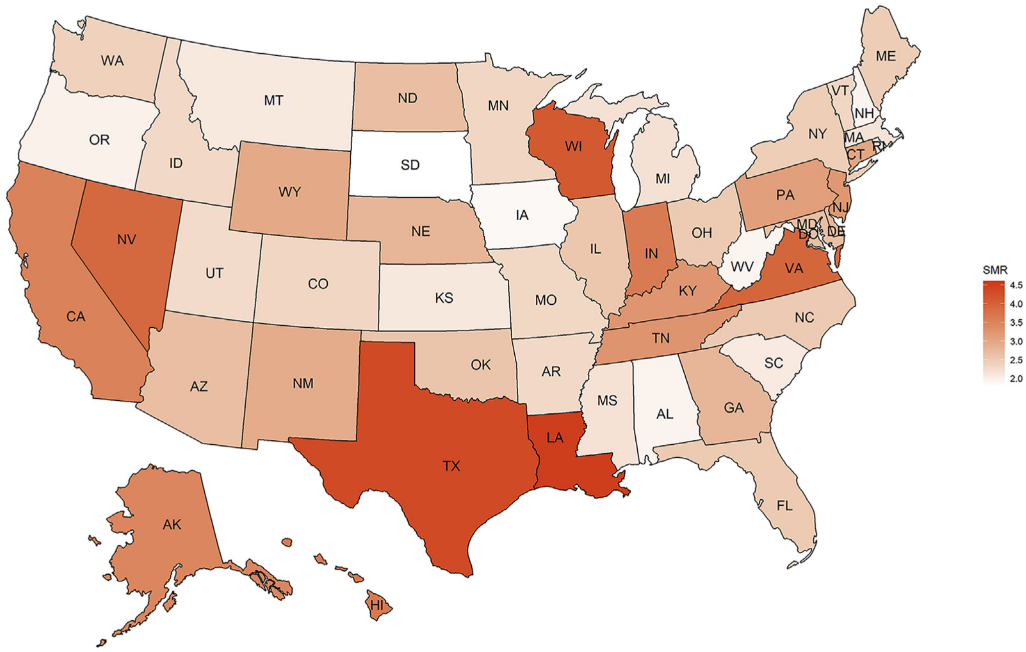

Figure 6. Heat map of United States illustrating standardized mortality ratios (SMR) by state. Numeric values available in Supplemental Table 3.

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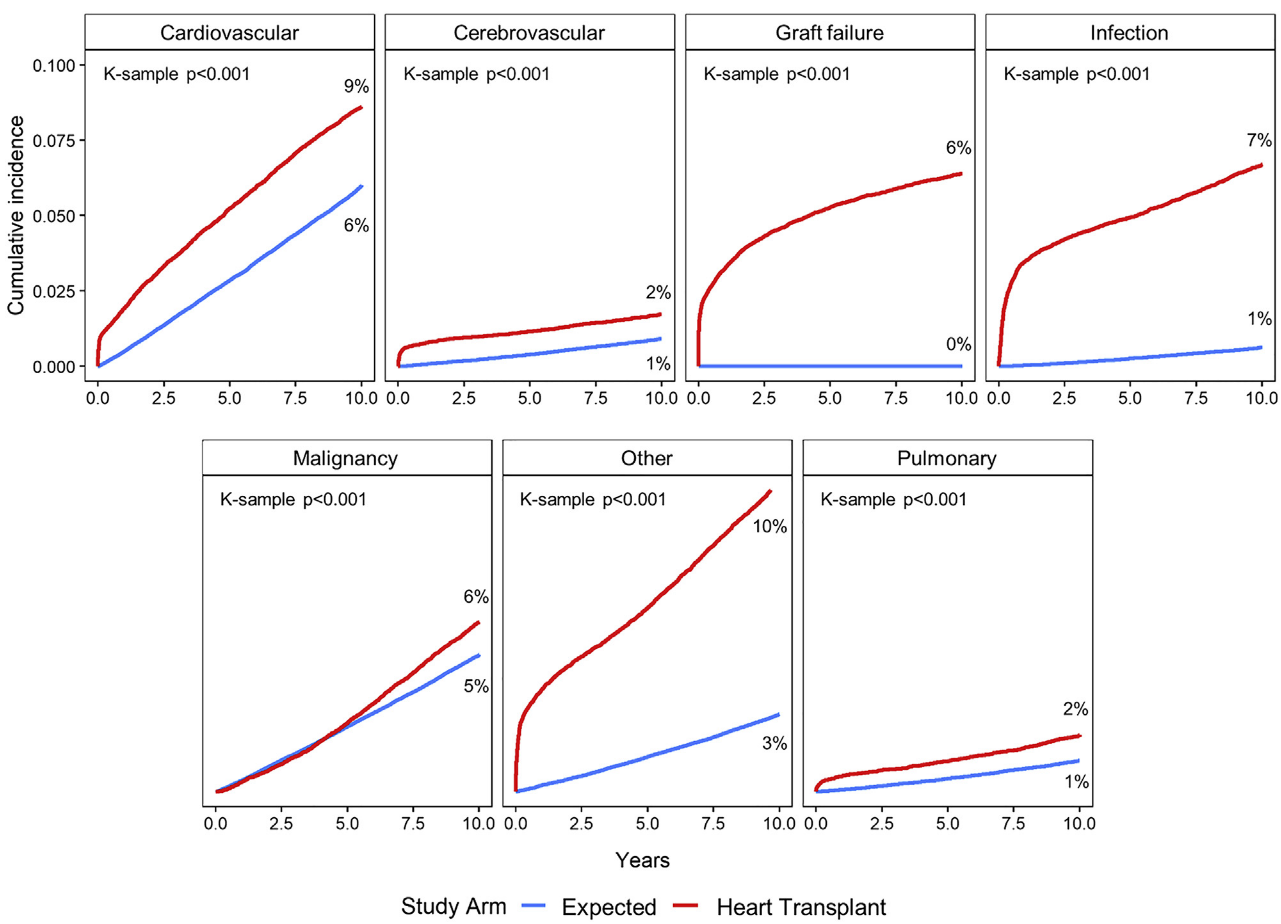

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Figure 7. Competing outcomes analysis of the cause of death as a function of time after heart transplantation. Differences in cumulative incidences were tested by the K-sample Anderson-Darling test. Study arm: expected (blue line); heart transplant (red line).

separation between the observed and expected incidence of death from infection. This finding is congruent with previous findings that report infection to be the most common cause of death within the first year.[25] However, the observed hazards of late death from infection were higher than expected, which may be reflective of prolonged immunosuppression therapy. The observed incidence of death from cerebrovascular causes is slightly higher than expected and appears to separate early after transplantation. One may speculate this separation occurs from perioperative stroke given that it is consistent with reported rates, which range between 1% and 2%.[26,27] Prior studies described higher standardized incidence ratios of de novo malignancy after solid organ transplantation.[28] Heart recipients are at a greater risk of malignancy than other solid organ recipients,[24] which may be reflective of the higher degree of immunosuppression therapy utilized.[29,30] Considering these concepts, the authors found it remarkable that increased incidence only translated to a 20% increase in standardized mortality (at 10 years, observed 6% vs expected 5%). Perhaps the cumulative incidence of death from malignancy is higher 10 to 20 years after transplantation.

Study Limitations

Case-control studies are susceptible to selection and reporting bias. Selection bias was minimized by utilizing a nested study design and selecting control subjects with similar demographic characteristics. However, characteristics that may have an association with long-term survival, such as socioeconomic distress or burden of noncommunicable diseases, were not available for subject matching. The likelihood of reporting bias in this study is minimal given that the primary endpoint—patient survival—was obtained by tracking death certificates from national agencies, such as the National Center for Health Statistics or the Social Security Administration. The Organ Procurement and Transplantation dataset corresponds to the entire population of patients who underwent heart transplantation in the United States during the study period, whereas the NLMS only comprehends a sample of the entire US population. These results are valid under the assumption that the NLMS accurately represents survival in the US population and that the possibility for selection bias in this survey is negligible.

Conclusion

Heart transplant recipients have considerable long-term survival and a threefold higher standardized long-term mortality rate than that of the noninstitutionalized population. Long-term mortality rates have consistently declined over time and will likely continue to decrease. Standardized mortality varies greatly across age, sex, and racial groups.

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Observed Versus Expected Survival After HTX: Is the Cup Half Full or Half Empty?

Invited Commentary:

In this issue of *The Annals of Thoracic Surgery*, the study by Suarez-Pierre and colleagues[1] is a well-conducted nested case-control study that provides insights into standardized mortality rates (SMR) of heart transplant (HTX) recipients in the United States between 1990 and 2007. Overall SMR after HTX was 2.84, declining in more recent times to 2.58. Women, blacks, and Hispanics had higher SMR, and with increasing patient age, SMR decreased. Strikingly, there was considerable SMR variation among US states. As expected, cardiovascular death, graft failure, and infection were found to be important causes of excess mortality starting right after HTX, and excess mortality due to malignancy becomes obvious (as expected) beyond 5 years after HTX. Although it is good to see SMR decline with time, the observed SMR variation in different patient groups and across different US states is worrisome and poses the question whether the cup is half full or half empty.

The observed temporal declines in SMR in more recent years can in part be explained by modestly better observed 1-year survival since 2001 and in part by modestly but steadily improving long-term survival rates since the mid 1990s (Supplemental Figures 4, 7), reflecting improvements in perioperative and long-term postoperative management after HTX.[1] However, the observed lower SMR in more recent years may also be due to the control group consisting of a sample of the National Longitudinal Mortality Study, a study conducted between the late 1980s and early 1990s. During the study period (January 1990 to December 2007), the average US life expectancy increased from 75 to 78 years, and this increase in life expectancy was not taken into account in the current study.

Zooming in on patient subgroups: the observation that SMR decreases with increasing patient age is a well-known phenomenon in cardiac surgery, probably reflecting stricter HTX acceptance criteria for older patients and a more serious heart disease phenotype in younger patients. I disagree with the statement by Suarez-Pierre and colleagues[1] in the discussion that most likely the increased SMR among young recipients, female recipients, and Hispanic recipients is high largely due to the control demographic that these recipients are being compared with, as these recipients have a relatively high life expectancy in the US population. If this would be true, then what would be the explanation for the increased SMR among blacks recipients? In my view, it is not so simple, and complex underlying factors—including biological, sex, and socioeconomic factors (access to HTX for one)—undoubtedly play a role. Add to this the fascinating and eye-opening Figure 6, showing significant SMR variability among US states,[1] and one realizes that the cup is half full and half empty at the same time, and many challenges are ahead to unravel the mechanisms underlying the observed variability in outcomes. Insights into these mechanisms will pave the way toward sustainable further improvement in HTX outcomes for all patients, young and old, male and female, regardless of race or geographic location.

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