

Original Investigation

Survival Benefit of Solid-Organ Transplant in the United States

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IMPORTANCE The field of transplantation has made tremendous progress since the first successful kidney transplant in 1954.

OBJECTIVE To determine the survival benefit of solid-organ transplant as recorded during a 25-year study period in the United Network for Organ Sharing (UNOS) database and the Social Security Administration Death Master File.

DESIGN, SETTING, AND PARTICIPANTS In this retrospective analysis of UNOS data for solid-organ transplant during a 25-year period (September 1, 1987, through December 31, 2012), we reviewed the records of 1 112 835 patients: 533 329 recipients who underwent a transplant and 579 506 patients who were placed on the waiting list but did not undergo a transplant.

MAIN OUTCOMES AND MEASURES The primary outcome was patient death while on the waiting list or after transplant. Kaplan-Meier survival functions were used for time-to-event analysis.

RESULTS We found that 2 270 859 life-years (2 150 200 life-years from the matched analysis) were saved to date during the 25 years of solid-organ transplant. A mean of 4.3 life-years were saved (observed to date) per solid-organ transplant recipient. Kidney transplant saved 1 372 969 life-years; liver transplant, 465 296 life-years; heart transplant, 269 715 life-years; lung transplant, 64 575 life-years; pancreas-kidney transplant, 79 198 life-years; pancreas transplant, 14 903 life-years; and intestine transplant, 4402 life-years.

CONCLUSIONS AND RELEVANCE Our analysis demonstrated that more than 2 million life-years were saved to date by solid-organ transplants during a 25-year study period. Transplants should be supported and organ donation encouraged.

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The earliest record of organ transplants is in the fourth century BC, when a surgeon named Tsin Yue-Jen exchanged the hearts of 2 soldiers.¹ In the 1940s, the groundbreaking experimentation in skin transplants of Medawar² and Merrill et al³ established the new field of transplantation immunology. Although other surgeons had attempted deceased-donor and living-donor kidney transplants, Joseph Murray, MD, performed the first successful kidney transplant in 1954 between identical twins, ushering in the new field of solid-organ transplantation.^{4,5} Soon after came a succession of firsts, all remarkable technical achievements: the first successful lung transplant performed by James Hardy, MD, in 1963,⁶ the first successful pancreas transplant performed by Richard Lillehei, MD, in 1966,⁷ the first successful liver transplant performed by Thomas Starzl, MD, in 1967,⁸

and the first successful heart transplant performed by Christiana Barnard, MD, in 1967.⁹

Cyclosporine, an immunosuppressive agent discovered in the 1970s and approved by the Food and Drug Administration in 1983, brought the field of solid-organ transplantation out of the realm of the experimental.¹⁰⁻¹⁴ From that point on, the number of transplants steadily increased, and the field was met with wider acceptance. In the late 1980s, the first successful bowel transplants¹⁵ and the first successful living-donor liver transplants¹⁶ were performed. The field of solid-organ transplantation, as we currently know it, began to take shape.

As the field expanded, a critical organ shortage quickly developed. In response, the US Congress passed the National Organ Transplant Act in 1984, which established the Organ Procurement and Transplantation Network under the United

Network for Organ Sharing (UNOS) to maintain a national registry for organ matching. A comprehensive national database soon emerged, recording information on all types of solid-organ transplants from 1987 on. In this study, we used the UNOS database to determine the survival benefit of 25 years of solid-organ transplants to mark the achievement of this marvel of modern medicine.

Methods

Study Population

In our retrospective analysis of UNOS, deidentified, patient-level data, we reviewed the records of all patients listed for a solid-organ transplant from September 1, 1987, through December 31, 2012 (n = 1 112 835). Institutional review board approval is not necessary for deidentified data from the UNOS database. We followed up all patients from the time of their UNOS listing: 533 329 recipients who underwent a transplant and 579 506 patients who were placed on a waiting list but did not undergo a transplant. The adult analysis excluded patients who were younger than 18, whereas the pediatric analysis excluded patients who were 18 years and older. There were no other exclusions within the categories listed. Only primary transplants were included in the categories listed, with the exception of the additional transplant categories for which the patients had only one prior transplant. Multiple additional transplants and sequential transplants (n = 17 402) were not included. Also excluded, because of insufficient numbers for analysis, were recipients of the following transplant types: liver-heart (n = 170), liver-lung (n = 55), heart-pancreas (n = 5), pediatric heart-kidney (n = 19), lung-kidney (n = 24), lung-pancreas (n = 3), intestine-kidney (n = 123), additional intestine transplant (n = 74), additional intestine-liver transplant (n = 83), pediatric pancreas-kidney transplant (n = 13), pediatric pancreas transplant alone (n = 8), and pediatric pancreas transplant after kidney transplant (n = 2).

Posttransplant deaths are recorded in the UNOS database; we supplemented that resource with the Social Security Administration Death Master File. To establish deaths of patients on the waiting list, we used the Social Security Administration Death Master File; we supplemented that resource with the death date recorded in the UNOS database and/or with the date of waiting-list deactivation when a patient was deemed too ill for a heart, lung, or liver transplant. Because death was primarily established by the Social Security Administration Death Files and all patients were followed up from the date of listing, deactivation from the list did not affect the analysis.

In our analyses, we grouped intestine-liver transplants with intestine transplants because of their similar outcomes (rather than with liver transplants).¹⁷ For the same reason, we grouped heart-lung transplants with lung transplants (rather than with heart transplants).¹⁸

Statistical Analysis

To analyze the data, we used STATA statistical software, version 12 (Stata Corp). To compare continuous variables (re-

ported as mean [SD]), we used the *t* test. To compare categorical variables, we used contingency tables. Results were considered significant at $P < .05$. All reported *P* values were 2-sided.

For our time-to-event analysis, we used the Kaplan-Meier method with a log-rank test. We censored patients who were either lost to follow-up or alive on December 31, 2012. We generated Kaplan-Meier curves for waiting-list survival from the time of UNOS listing to death. Because we used the Social Security Administration Death Master File, patients lost to UNOS follow-up did not affect our analysis. We generated Kaplan-Meier curves for posttransplant survival from the time of transplant to death. The primary outcome measure was patient death while on the waiting list or after the transplant.

Life-years Saved

We calculated the life-years saved by comparing patients who were on the waiting list but did not undergo a transplant with patients who did. We compared survival for both groups from a common time point, namely, the time of listing. We first generated the total number of life-years for all patients on the waiting list who did not undergo a transplant by calculating the area under the Kaplan-Meier curve. We further calculated the number of life-years for those who did not undergo a transplant also using the area under the Kaplan-Meier curve. After adjusting for the number of patients, we then calculated the number of life-years saved.

Median Survival

For the groups of patients who did not achieve median survival time by the end of the study period, we recorded their median survival time as greater than 25 years rather than risk an inaccurate projection.

Era Analysis

We defined 3 eras for analysis: 1987 through 1993, 1994 through 2001, and 2002 through 2012. The first dividing year was 1994 because of Food and Drug Administration approval that year for the clinical application of tacrolimus. The second dividing year was 2002 because of allocation policy shifts. We only included lung transplants in this analysis because that group had the poorest outcomes and a controversial survival benefit. Our aim was to show improved outcomes over time.

Propensity Score Matching

Because there is a selection bias with the transplanted cohort, we used a propensity score matching algorithm to generate matched cohorts for comparison. The propensity score for the transplant group was computed with a probit regression for specific covariates in each type of organ transplant. For kidney transplant, we included the following covariates: blood type, age at listing, region of listing, date of listing, dialysis at listing, date that dialysis was started, and diagnosis. For liver transplant, we included the following covariates: blood type, age at listing, region of listing, date of listing, status at the time of listing, Model for End-Stage Liver Disease score at listing, hemodialysis at listing, and diagnosis. For heart transplant, we included the following covariates: blood type, age

Table 1. Survival Benefit of Solid-Organ Transplant

Transplant Type and Patient Category	No. of Patients	No. of Life-years	Observed No. of Life-years Saved to Date	Observed No. of Life-years Saved per Patient to Date	Median Survival, y
Kidney					
Waiting list	355 189	987 009	... ^a	...	5.4
Transplant	314 561	2 246 383	1 372 969	4.4	12.4
Liver					
Waiting list	134 826	218 026	3.1
Transplant	112 319	659 637	465 296	4.3	11.6
Heart					
Waiting list	40 253	65 011	2.3
Transplant	54 746	358 555	269 715	4.9	9.5
Lung					
Waiting list	24 688	43 564	2.3
Transplant	26 943	116 301	64 575	2.6	5.2
Pancreas-kidney					
Waiting list	14 195	33 979	4.2
Transplant	16 995	119 620	79 198	4.6	14.5
Pancreas					
Waiting list	8568	26 733	8
Transplant	6177	34 193	14 903	2.4	13.3
Intestine					
Waiting list	1787	2086	1.8
Transplant	1588	6256	4402	2.8	5.1
Total					
Waiting list	579 506	1 376 408
Transplant	533 329	3 540 945	2 270 859	4.3	...

^a Ellipses indicate data not meaningful.

at listing, region of listing, date of listing, status at the time of listing, dialysis at listing, diagnosis, ventricular assist device at listing, extracorporeal membrane oxygenation at listing, and intra-aortic balloon pump at listing. For lung transplant, we included the following covariates: blood type, age at listing, region of listing, date of listing, status at the time of listing, dialysis at listing, diagnosis, forced expiratory volume in 1 second at listing, and oxygen requirement at listing. In pancreas-kidney transplant, we included the following covariates: blood type, age at listing, region of listing, date of listing, dialysis at listing, date that dialysis was started, and diagnosis. In pancreas transplant, we included the following covariates: blood type, age at listing, region of listing, date of listing, and diagnosis. In intestine transplant, we included the following covariates: blood type, age at listing, region of listing, date of listing, dialysis at listing, date that dialysis was started, diagnosis, waiting list for an intestine-liver transplant, and intestine-liver transplant. Total parenteral nutrition dependence could not be used because it was not reliably recorded for patients on the waiting list.

Propensity scores were then used to match patients undergoing transplants with patients on the waiting list using full Mahalanobis matching algorithm. The Mahalanobis distance is a descriptive metric that provides a measure of a data point's relative distance from a common point. A nearest neighbor search was then used to create matched groups.

Results

Study Population

During the study period (September 1, 1987, through December 31, 2012), a total of 1 112 835 patients were placed on the waiting list for a solid-organ transplant: 533 329 recipients who underwent a transplant and 579 506 patients who were on the waiting list but did not undergo a transplant. A total of 314 561 patients underwent kidney transplants; 109 482 patients, liver transplants; 54 746, heart transplants; 26 943, lung transplants; 23 709, pancreas transplants; and 1588, intestine transplants. **Table 1** summarizes the demographic characteristics.

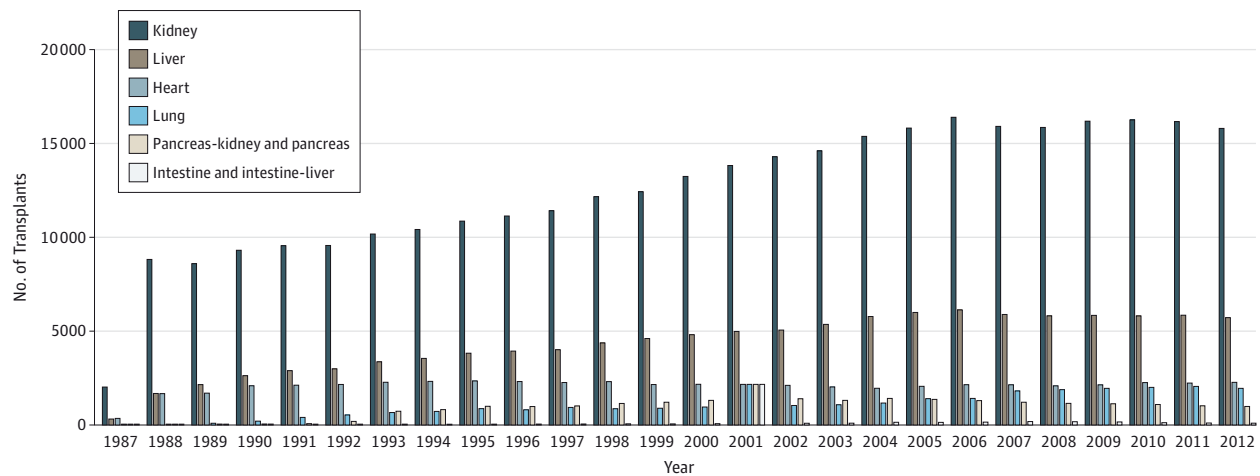
Transplant Volume

Figure 1 represents the transplant volume by organ type per year. The peak volumes were in 1995 for heart transplants; 2006 for kidney, liver, and pancreas transplants; 2007 for intestine transplants; and 2011 for lung transplants.

Life-years Saved

Table 1 and eTable 1 in the Supplement list the number of life-years saved by organ and transplant type through December 31, 2012. The total number of life-years saved for the 25-year study period will not be realized until all recipients during that period are deceased. However, so far, 1 372 272 life-years have

Figure 1. Solid-Organ Transplants in the United States



been saved by kidney transplants (4.4 life-years per recipient), 475 511 life-years by liver transplants (4.3 life-years per recipient), 269 715 life-years by heart transplants (4.9 life-years per recipient), 68 758 life-years by lung transplants (2.6 life-years per recipient), 79 198 life-years by pancreas-kidney transplants (4.6 life-years per recipient), 14 903 life-years by pancreas transplants (2.4 life-years per recipient), and 4402 life-years by intestine transplants (2.8 life-years per recipient). eTable 1 in the Supplement also lists the median survival time by organ and transplant type.

Kaplan-Meier Curves

Figure 2 and eFigures 1 through 5 in the Supplement show the survival curves for patients on the waiting list vs transplant recipients by organ and transplant type. During the 25-year study period, posttransplant survival time was significantly better than waiting-list survival time, with the exceptions of additional pediatric liver transplant, pediatric lung transplant, pediatric heart-lung transplant, and pediatric intestine transplant recipients. eFigure 6 in the Supplement illustrates improved outcome by era (1987-1993, 1994-2001, and 2002-2012) for adult and pediatric lung transplant recipients.

Propensity Score Matching

Table 2 gives the results of the propensity score matching. The number of matched patients and the median survival are listed. If we adjust life-years saved by the results of the matched analysis, the result is 2 150 200 life-years saved.

Discussion

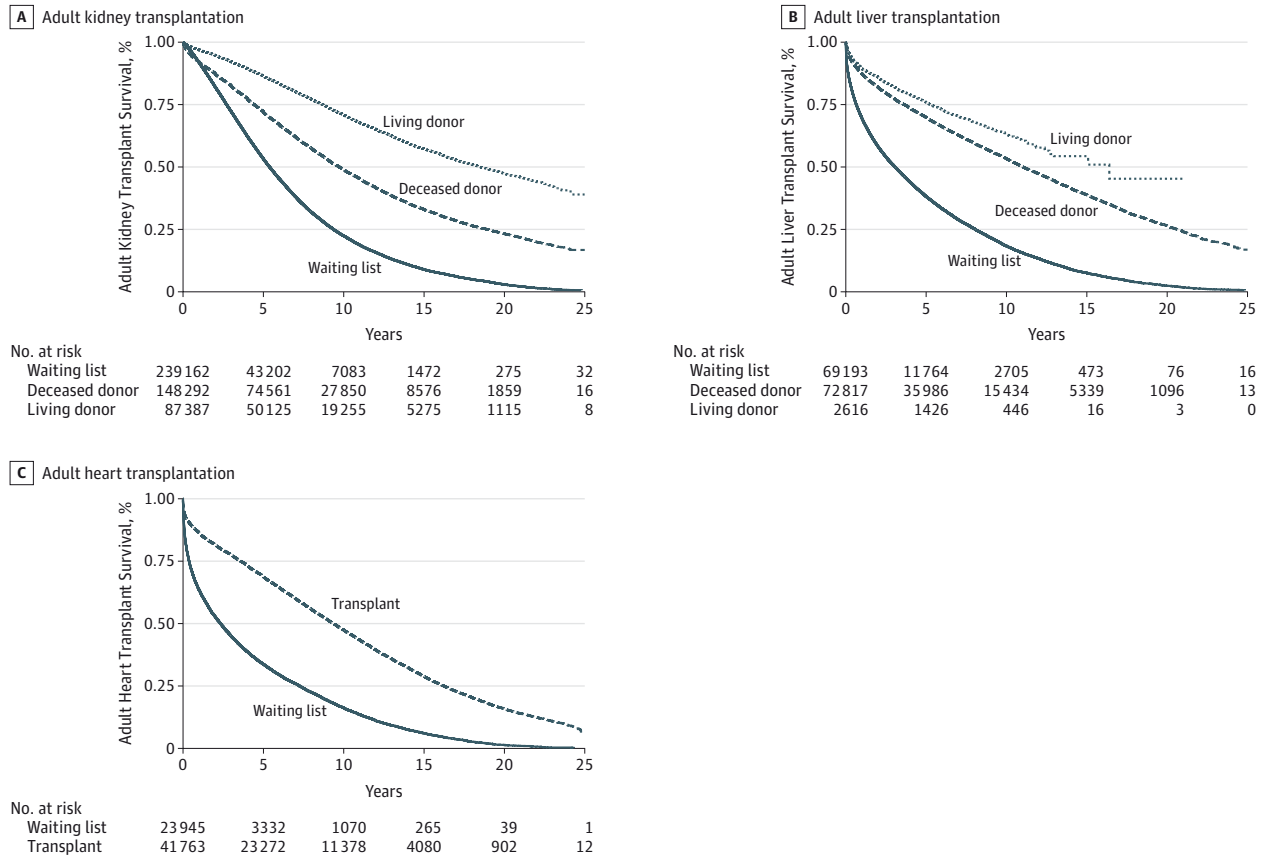
It was not until the late 20th century, after a series of breakthroughs, that the field of transplantation had practical implications with significant therapeutic value.^{2-4,10-14,19} In our study, we documented the survival benefit of solid-organ transplants during a 25-year period (1987-2012)—a period that has seen unprecedented growth and improved outcomes in kid-

ney, liver, heart, lung, pancreas, intestine, and combined organ transplants. We found that 2 270 859 life-years were saved in 533 329 patients through 2012. Because many of the transplant recipients in our study group are still alive, the number of life-years saved, thanks to this 25-year period of transplantation, will only increase until all the recipients in the cohort are deceased. This concept becomes readily apparent with the significant differences in the median survival time between patients on the waiting list and transplant recipients. Our study included any patient who was ever listed for a solid-organ transplant from 1987 through 2012 (n = 1 112 835 patients): only 533 329 (47.9%) of them actually underwent a solid-organ transplant.

This immense study illustrates the powerful potential of the UNOS database. The comprehensive UNOS reporting of all waiting-list patients, coupled with death verification using the Social Security Administration Death Master File, made this analysis possible. Without the Social Security Administration Death Master File, our analysis would have been crippled by the significant number of patients lost to UNOS follow-up. Beginning on January 1, 2013 (the day after the end of the study period), the Social Security Administration Death Master File was no longer being shared with UNOS because of patient privacy issues. We hope that our study illustrates how essential the Social Security Administration Death Master File is to the complete analysis of posttransplant survival. We call for the reversal of this mandate and for the renewed sharing of the Social Security Administration Death Master File to help advance studies of solid-organ transplants.

A kidney transplant is often thought to be merely a life-enhancing (rather than lifesaving) procedure in that recipients are simply relieved of the requirement of dialysis. However, as other studies²⁰⁻²² have done in the past, our study clearly indicated that a kidney transplant is also a lifesaving procedure. The number of life-years saved per kidney transplant recipient is akin to the number of life-years saved per liver transplant recipient. Our study also found a profound advantage for adult kidney transplant recipients of living-donor trans-

Figure 2. Survival for Adult Patients Undergoing Kidney, Liver, and Heart Transplants



Included are patients on the waiting list and recipients of living-donor and deceased-donor transplants. A, Adult kidney transplantation; B, adult liver transplantation; C, adult heart transplantation. $P < .001$ for waiting list vs deceased-donor transplants, waiting list vs living-donor transplants, and deceased-donor vs living-donor transplants (log-rank test).

plants compared with deceased-donor transplants.^{23,24} This advantage is evident in the Kaplan-Meier curves (Figure 1 and eFigures 1-5 in the Supplement) and in the median survival time (18.5 years with a living donor vs 9.8 years with a deceased donor). However, the advantage is not so pronounced for pediatric kidney transplant recipients (eTable 1 in the Supplement).

In the same vein, a pancreas transplant is also a lifesaving procedure. The perception persists that a pancreas transplant is simply a convenient insulin replacement therapy, despite much evidence in the literature to the contrary.²⁴⁻²⁷ Our study found a significant survival advantage for all types of pancreas transplants, with the strongest advantage for simultaneous pancreas and kidney transplant recipients (4.7 life-years per recipient). A pancreas transplant alone, an often controversial option,²⁸ confers a median survival time of 13.6 years (compared with 8 years in patients on the waiting list). Our survival curves demonstrate how the survival benefit becomes more pronounced with long-term follow-up (eFigure 3 in the Supplement). There was an earlier controversy about the use of pancreas transplant alone in studies with 5 years of follow-up.^{28,29} In our study, the follow-up time was up to 20

years; our findings unequivocally confirm the utility of a pancreas transplant alone.

Our study also reaffirms the lifesaving potential of a liver transplant.³⁰ The use of liver retransplantation has often been questioned,³¹ but we found a significant survival advantage (although diminished compared with a primary liver transplant). We also revealed the durability of a successful pediatric liver transplant: with all types (whole-organ deceased donor, partial-organ deceased donor, and living donor), the median survival time exceeded 25 years. Such long-term survival is an amazing feat that is unmatched by most other types of transplant.^{32,33}

The past 3 decades of heart transplantation have demonstrated a clear survival benefit^{34,35} for adult and pediatric heart transplants.³⁶ Moreover, advances in the care of patients with heart failure, especially through the use of artificial devices, have gradually improved survival time in patients on the waiting list.^{37,38} Additional transplants also are useful, but their usefulness is diminished compared with primary transplants.^{39,40}

Previous studies^{41,42} found a survival benefit for adult lung transplant recipients. In our study, we reached a similar conclusion. However, unlike most of the literature,^{18,43,44} we found

Table 2. Survival Benefit of Solid-Organ Transplant After Propensity Score Matching

Transplant Type and Patient Category	No. of Patients	Unadjusted Median Survival, y	No. of Patients After Matching	Median Survival After Matching, y
Kidney				
Waiting list	355 189	5.4	173 086	5.3
Transplant	314 561	12.4	112 049	12.1
Liver				
Waiting list	134 826	3.1	86 050	2.9
Transplant	112 319	11.6	64 011	10.1
Heart				
Waiting list	38 578	2.3	31 086	2.7
Transplant	54 039	9.5	53 173	9.5
Lung				
Waiting list	24 688	2.3	8960	2.1
Transplant	26 943	5.2	9934	4.9
Pancreas-kidney				
Waiting list	14 195	4.2	7134	3.7
Transplant	16 995	14.5	6713	14.4
Pancreas				
Waiting list	8568	8	7010	7.8
Transplant	6177	13.3	6042	14.5
Intestine				
Waiting list	1787	1.8	1185	1.9
Transplant	1588	5.1	802	5.0
Total				
Waiting list	577 831	... ^a	314 511	...
Transplant	532 622	...	252 724	...

^a Ellipses indicate data not meaningful.

that double-lung transplant recipients fared better than single-lung transplant recipients, perhaps because of our study's longer follow-up.⁴⁵ As with lung transplant recipients, a previous study,¹⁸ as well as our study, confirmed a survival benefit for adult heart-lung transplant recipients. However, the picture remains more ambiguous for pediatric lung and pediatric heart-lung transplant recipients, without a clear survival benefit.⁴⁶ Our analysis suggested a significant survival benefit for both these categories but largely because of a greater number of long-term survivors during the 25-year study period; however, our Kaplan-Meier curves were not significantly different, and the median survival time for patients on the waiting list in those 2 categories was longer than the post-transplant survival time. The real benefit may be life-enhancing rather than lifesaving. The time span of our analysis was considerable: 25 years. When we stratified groups by the 3 eras, we saw considerable improvement in adult and pediatric lung transplant recipients. The survival benefit for pediatric lung transplant recipients may, in fact, be evolving and not able to be sufficiently addressed by an all-inclusive study such as ours. More sophisticated analyses with stratification by age of the child⁴⁷ and diagnosis^{48,49} may be necessary to elucidate the potential survival benefit.

Intestine transplant is also a lifesaving procedure.^{50,51} The survival benefit is also more pronounced in the intestine-liver transplant recipients, not because of improved posttransplant survival but rather because of the higher mortality rate in patients with end-stage liver disease on the waiting list.^{17,52,53}

In fact, patients with intestine failure are often maintained with total parenteral nutrition until they develop end-stage liver disease; they are then placed on the waiting list for a liver intestine transplant and removed from the intestine transplant alone list. This association between the 2 waiting lists may explain the limited mortality rate of pediatric patients awaiting an intestine transplant alone (eTable 1 in the Supplement). We are not suggesting that patients should undergo an intestine-liver transplant rather than an intestine transplant alone. Instead, we assert that because the mortality rate is much higher on the intestine-liver waiting list, the survival benefit after transplant is more pronounced. Of note, other studies^{17,54} have suggested that an early intestine transplant alone may yield superior overall outcomes. As with lung transplant recipients, the survival benefit for intestine transplant recipients may be evolving. The literature suggests an improvement in outcomes over time.⁵⁵⁻⁵⁷

There is a selection bias with those candidates who undergo transplants. This bias is apparent in the differences in the demographic data (eTable 2 in the Supplement). To overcome this bias, we conducted sophisticated matching with propensity scores and found that a significant survival benefit was still observed (Table 2). After adjusting for our matched analysis, we calculated 2.15 million life-years saved to date. A significant selection bias is likely to remain, even after propensity score matching, and is a limitation of this analysis. Another limitation of this analysis is the bias introduced by the waiting time for patients who undergo transplants. They, by defi-

nition, had to survive their time on the waiting list. A third limitation is the variable entry completion by era, limiting the effectiveness of our propensity score matching.

Conclusions

The 2.3 million life-years saved (2.15 million after adjustment) to date is a stellar accomplishment. These life-years saved are in patients with end-organ failure, who are among the sickest patients. Of note, the life-years saved were observed; there are no projections in this analysis. Although most of the findings in this analysis are not novel, this analysis concisely reports on the collective experience of solid-organ transplant in the United States, making it, to our knowledge, the larg-

est study in the field of transplantation yet conducted. These results refute any lingering perception of transplantation as a niche field with limited practical benefit. Furthermore, focusing exclusively on the survival benefit does not capture the vast improvements in quality of life and the drastically lowered morbidity rates after a transplant.

Our analysis indicated that, as a nation, we achieved the peak volume in transplantation in 2006. The critical shortage of donors continues to hamper this field: only 47.9% of patients on the waiting list during the 25-year study period underwent a transplant. The need is increasing; therefore, organ donation must increase. We call for deepened support of solid-organ transplant and donation—worthy endeavors with a remarkable record of achievement and a tremendous potential to do even more good for humankind in the future.

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