JOURNAL OF INSURANCE MEDICINE

J Insur Med 2024;51:163–170

REVIEW

The Survival Benefit of Pancreas Transplantation: Considerations for Insurance Coverage

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Key words: Pancreas transplantation, survival benefit, insurance coverage, kidney transplants alone (KTA), waiting list, mortality, life-years, life-years saved.

Received: July 9, 2024

Accepted: July 11, 2024

The first pancreas transplant was performed by William Kelly and Richard Lillehei at the University of Minnesota on December 17, 1966, but high graft failure rates initially marred the field of pancreas transplantation due to technical and immunological complications. For that reason, until the early 1980s, less than 100 pancreas transplants per year were performed worldwide. With major improvements in surgical techniques and immunosuppressive therapy that number had increased to 1000 pancreas transplants per year in the early 1990s and to >2000 pancreas transplants per year after the turn of the millennium. By the end of 2020, more than 63,000 pancreas transplants had been performed worldwide with an average of 2300 transplants per year from 2010 to 2020. Despite this increase, the number of pancreas transplants has continued to substantially trail those of kidney and liver transplants. For that reason, survival benefit analyses of pancreas transplantation have also lagged those for kidney and liver transplantation.[1–4] In the past, only a few studies have systematically analyzed the survival benefit of pancreas transplantation.

LIFE-ENHANCING VS LIFE-SAVING TRANSPLANTS

Survival benefit studies have resulted in a better understanding of life-enhancing vs life-saving transplants. Liver, heart, and lung transplants have always been considered life-saving procedures whereas kidney and pancreas transplantation were regarded as life-enhancing procedures.

In the case of kidney transplantation, the argument for merely a life-enhancing procedure was initially made because recipients are simply

relieved of the requirement of dialysis. However, the survival benefit of kidney transplant recipients vs transplant candidates on dialysis was clearly shown by Port et al. in the early 1990s.[2,5] Although the overall mortality risk following kidney transplantation was initially increased, there was a long-term survival benefit for transplant recipients compared with similar patients on dialysis. In a study published two decades later,[6,7] it was shown that a kidney transplant is also a lifesaving procedure: the number of life-years saved per kidney transplant recipient was akin to the number of life-years saved per liver transplant recipient. That same study also demonstrated a significant survival benefit for adult kidney transplant recipients of living-donor transplants compared with deceased-donor transplants:[8,9] the median survival time was 18.5 years with a living donor vs 9.8 years with a deceased donor.

Akin to kidney transplantation, a pancreas transplant must also be considered a lifesaving procedure.

For a long time, the perception has persisted that a pancreas transplant is simply an alternative to insulin replacement therapy, despite evidence in the literature to the contrary.[9–13] Unlike liver and heart transplants, pancreas transplants are usually not immediately lifesaving procedures.

However, their life-saving nature becomes evident within several months post-transplant by decreasing the recipients' risk of death from hypoglycemic unawareness, cardiocerebrovascular events, and other secondary diabetic complications.

METHODOLOGICAL SURVIVAL STUDY LIMITATIONS

From a statistical point of view, comparative survival benefit analyses are complex due to an intrinsic selection bias for those candidates who undergo transplants. To overcome this bias, some studies have conducted sophisticated matching with propensity scores. However, a significant selection bias may remain and must be considered a limitation. The selection bias is also complicated by differences in listing criteria for candidates and recipient categories according to individual transplant centers and physicians. Another limitation of such studies is the bias introduced by the waiting time for patients who undergo transplants. These transplant candidates, by definition, had to survive their time on the waiting list. A third limitation is the variable entry completion by era, limiting the effectiveness of propensity score matching.

Another consideration is that the content of the database must be meticulously surveyed to avoid incorrect conclusions based on unscrutinized information. This occurred in a survival study in recipients of solitary pancreas transplants that supposedly showed that survival was significantly worse compared with the survival of waiting-list candidates receiving conventional therapy.[14] Using the same database but eliminating patients with multiple listings at different transplant centers or with false or incomplete information showed the exact opposite result.[15] Lastly, direct group comparison between the 4 diabetic transplant categories (SPK, PTA, PAK, KTA) is difficult because of preexisting conditions and choice of transplant category.

SURVIVAL BENEFIT OF PANCREAS TRANSPLANTATION IN LITERATURE

Several single-center studies have shown a survival benefit for pancreas transplant recipients by comparing SPK with diabetic kidney transplant alone (KTA) recipients. A Dutch study by Smets et al[12] not only found that the hazard ratio for mortality after the start of renal-replacement therapy was significantly lower for SPK versus KTA recipients but also showed that the mortality ratio was lower for transplanted versus non-transplanted patients. A British study compared mortality between pancreas transplant recipients with a control group of patients on the waiting list. The authors noted a significantly higher waiting

list mortality of 30% compared with a mortality of 9% after transplantation. In addition, deaths on the waiting list compared with transplantation up to 1 year had a relative risk of 2.67, whilst those surviving >1 year had a relative risk of 5.89 of dying on the waiting list.[16] This finding is in line with an IPTR analysis that showed that the mortality risk of the transplant procedure itself is higher only within the first few months of the first transplant year (SPK, 59 days posttransplant; PAK, 80 days posttransplant; PTA, 230 days posttransplant) and then significantly decreases below the wait list mortality for the remainder of the first posttransplant year.[15]

The hitherto most comprehensive study of survival benefits after all types of solid organ transplants in the United States and covering a 25-year time period found a significant survival benefit for all types of pancreas transplants irrespective of the recipient category.[6] The strongest survival benefit was noted for SPK recipients (4.7 life-years per recipient). A PTA conferred a median survival time of 13.6 years (compared with 8 years in patients on the waiting list). The survival benefit became more pronounced with long-term follow-up. The authors also noted that there was an earlier controversy (as mentioned earlier) about the survival benefit of solitary pancreas transplants in studies with 5 years of follow-up.[14,15] In the Rana et al study, the follow-up time was up to 20 years; their findings unequivocally confirmed the survival benefits of solitary pancreas transplants in the PTA and PAK categories over wait-listed patients.[6]

SURVIVAL BENEFIT ACCORDING TO IPTR/UNOS

A new IPTR analysis determined the survival benefit for pancreas and/or kidney transplants based on the IPTR/UNOS database and the Social Security Administration Death Master File for the time period from 1/1/2000 to 5/31/2021. During that time period, 212,049 diabetic patients were listed for a primary deceased donor transplant. In total, 184,927 patients were listed for a KTA, 21,244 for a SPK, 3,512 for a PAK and 2,366 for a PTA. The distributions of the different diabetes categories are significantly different and are shown in Table 1. While diabetic patients listed for a KTA transplant are more likely to have type 2 diabetes mellitus, patients listed in the solitary pancreas categories (PTA and PAK) are more likely to be type 1 as are patients listed for a SPK transplant.

Table 1. 212,049 diabetic patients listed for a primary deceased donor kidney (KTA), pancreas after kidney (PAK), pancreas transplant alone (PTA) or simultaneous pancreas/kidney transplant (SPK) by diabetes type during 1/1/2000 and 5/31/2021

	KTA	SPK	PAK	PTA
N	184,927	21,244	3,512	2,366
Diabetes				
Type 1	9.1%	85.4%	90.9%	94.2%
Type 2	87.2%	13.9%	8.2%	4.3%
Other/Unknown	3.7%	0.7%	0.9%	1.5%

Overall, 89,579 diabetic patients underwent a pancreas and/or kidney transplant, and 122,470 patients were still on the waiting list, were taken off the list or had died while waiting. There were 69,041 KTA, 16,088 SPK, 2667 PAK and 1783 PTA recipients. Adjustments were made for multiple listings, incomplete information, and classifications. The primary outcome was patient survival while on the waiting list or after transplant adjusted for potential cofounders.

The overall wait list mortality for all listed diabetic patients regardless of their transplant status is shown in Figure 1; it was highest for SPK and KTA candidates. The median wait-list survival for all diabetic patients (type 1 and 2 diabetes) was 5.0 years for SPK, 5.8 years for KTA, 8.6 years for PAK, and 11.6 years for PTA candidates. By diabetes type, the median survival for patients listed with type 1 (vs type 2) diabetes mellitus was 4.9 (5.2) years for KTA, 5.0 (5.4) years for SPK, 8.6 (8.2) years for PAK, and 12.0 (-) years for

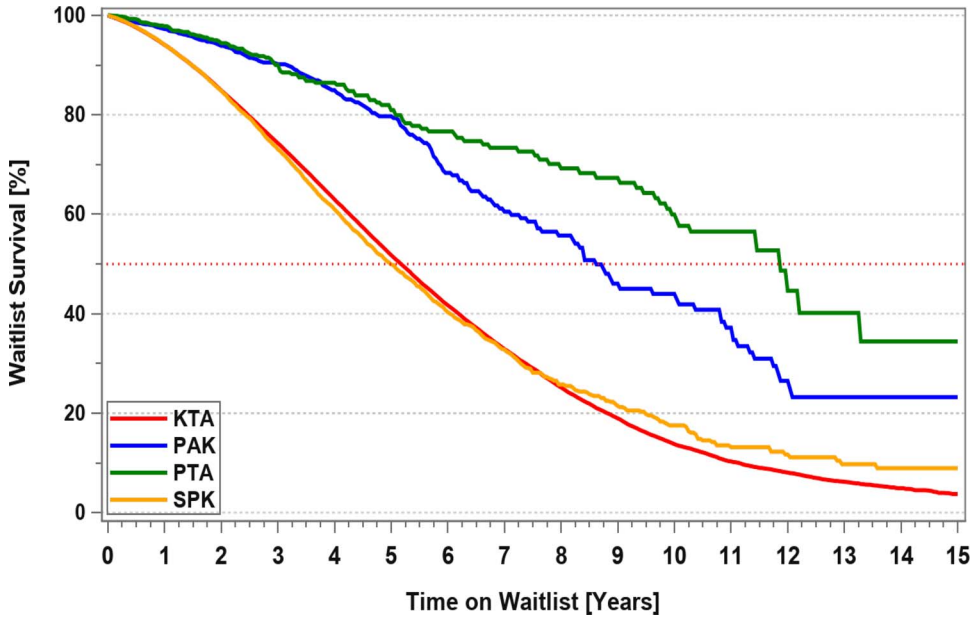

Figure 1. *Waitlist survival of 212,049 diabetic patients listed for a primary deceased donor kidney (KTA), pancreas after kidney (PAK), pancreas transplant alone (PTA), or simultaneous pancreas/kidney transplant (SPK) between 1/1/2000 and 5/31/2021.*

PTA candidates. Listings for PTA candidates with type 2 are very rare and the number of candidates is too low for analysis. The waitlist mortality of KTA and SPK listings was higher for patients with type 1 compared to patients with type 2 diabetes mellitus. Only in PAK listings was the mortality in type 2 candidates higher than in type 1 candidates.

A multivariable model for mortality risk assessment showed in all 4 categories a significant decrease in the mortality risk after transplantation compared to remaining on the waitlist. The highest risk reduction was achieved in the SPK category: it reduced the relative mortality risk by 94%. In the KTA category the relative mortality risk was reduced by 86%; in the PAK category, by 78%; and in the PTA category by 70%. The relative mortality risk was 25% lower in type 2 versus type 1 diabetic patients. Being on dialysis increased the relative waitlist mortality in the SPK category by 38% and by 21% in the KTA category. In all 4 categories, the relative mortality risk significantly increased with increasing age at listing.

To assess life-year saved, the patients who remained on the waitlist were used as control to assess the effect of the transplant. All computations were performed from the time of listing. To compute the life-years saved, the area under the survival curve for patients who remained on the waitlist is subtracted from the area under the survival curve for the patients who received a deceased donor transplant. Figure 2 shows the significant life-saving impact of a KTA compared to remaining on the waitlist. The median survival on the waitlist was 4.1 years compared to 11.6 years after receiving a KTA. Figure 3 shows the results in the SPK category. The median waitlist survival of 2.7 years compares to 17.0 years for patients who received the transplant. Figures 4 & 5 show the results for solitary pancreas transplants. The median survival on the waitlist is significantly higher than in the SPK category (6.7 years in the PAK and 11.4 years in the PTA categories). In contrast, for transplanted patients, the median survival time in the PAK category was 14.3 years and 18.3 years in the PTA category.

According to this IPTR analysis, primary deceased donor pancreas and/or kidney transplants in diabetic patients saved a total of 273,843 life-years: on average, 6.6 life-years per

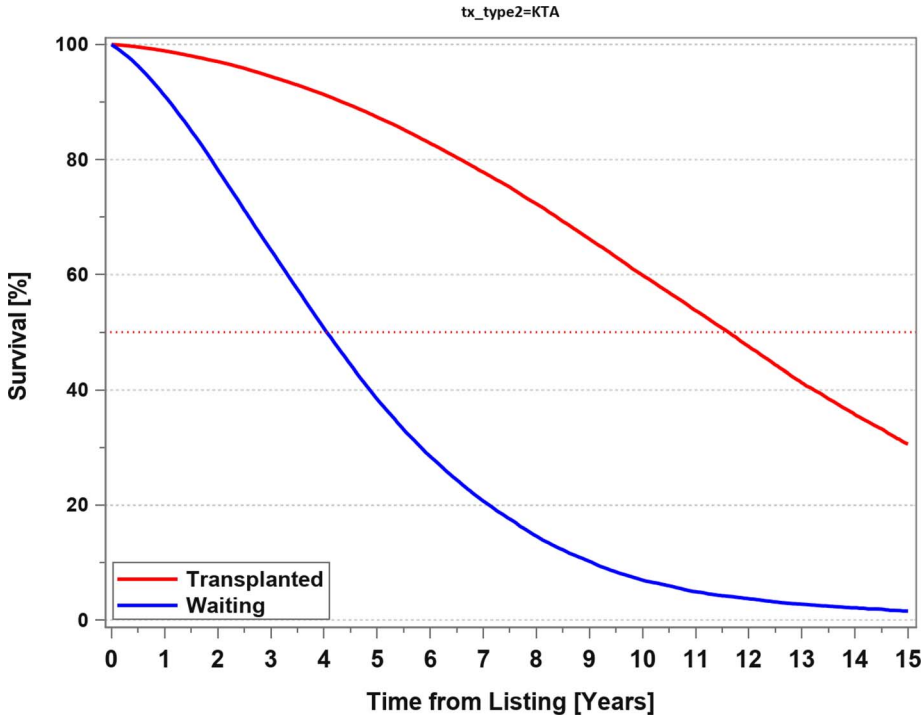

Figure 2. *KTA patient survival while on the waitlist vs transplanted between 1/1/2000 and 5/31/2021.*

patient were saved by KTA, 11.7 per patient by SPK, 6.3 per patient years by PAK, and 6.4 per patient by PTA transplants (Table 2). When the survival benefit only for patients with type 1 diabetes mellitus was computed, the average life-years saved for PAK remained the same but increased slightly for PTA (6.6 years) and SPK (11.9 years) transplants.

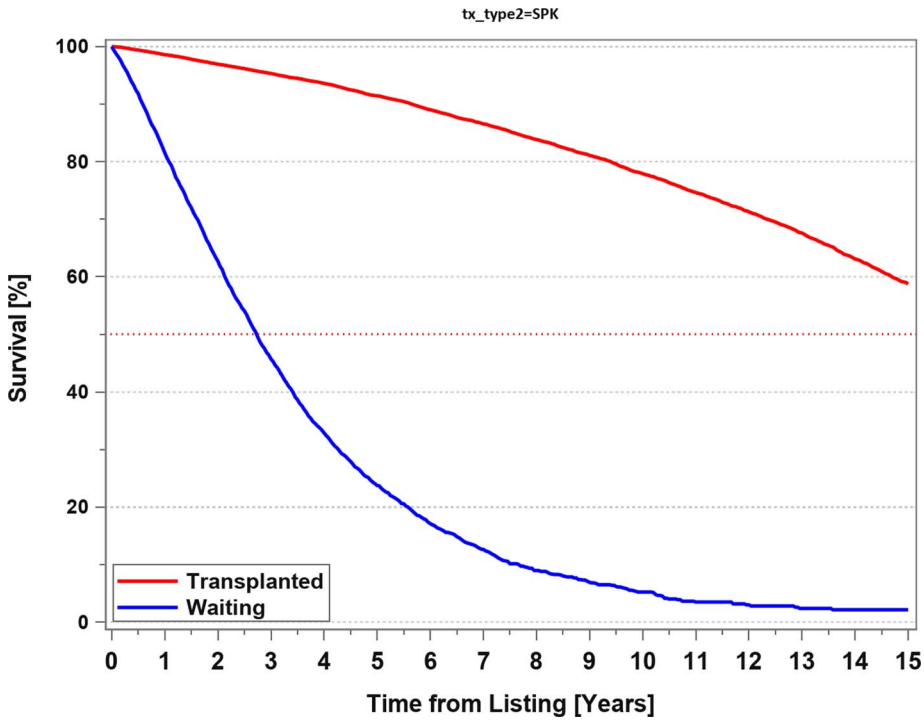

Figure 3. *SPK patient survival while on the waitlist vs transplanted between 1/1/2000 and 5/31/2021.*

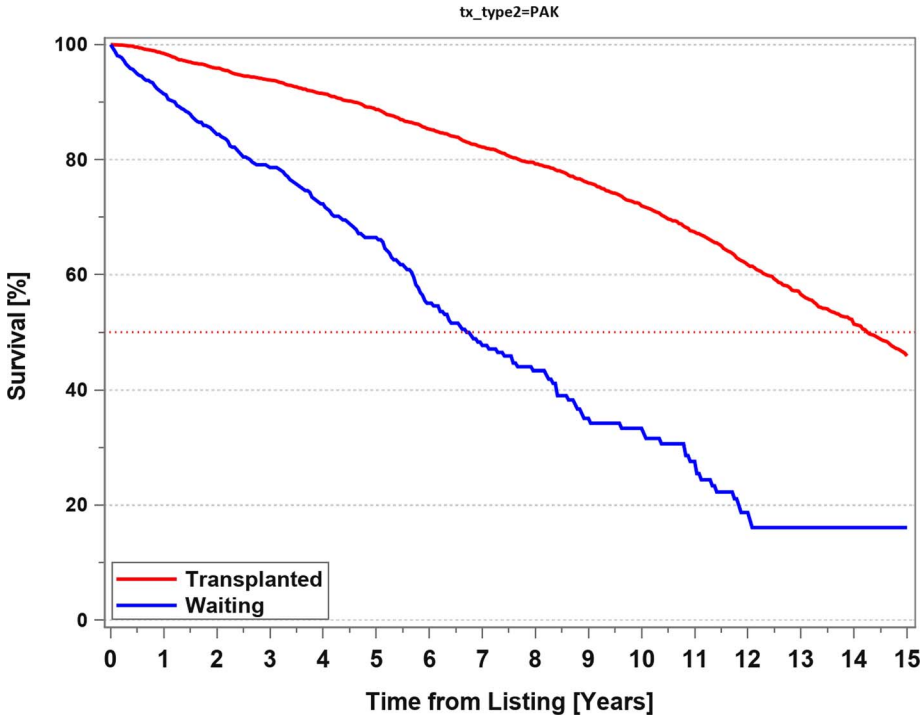

Figure 4. *PAK patient survival while on the waitlist vs transplanted between 1/1/2000 and 5/31/2021.*

For KTA transplants in patients with type 1 diabetes mellitus, the life-years saved per person increased to 8.2 years which was still lower compared to SPK recipients (Table 3).

In addition, the gain in life years has also had an impact on employment and societal re-integration: significantly more PTA and PAK versus SPK recipients worked for income after than before transplantation.[17]

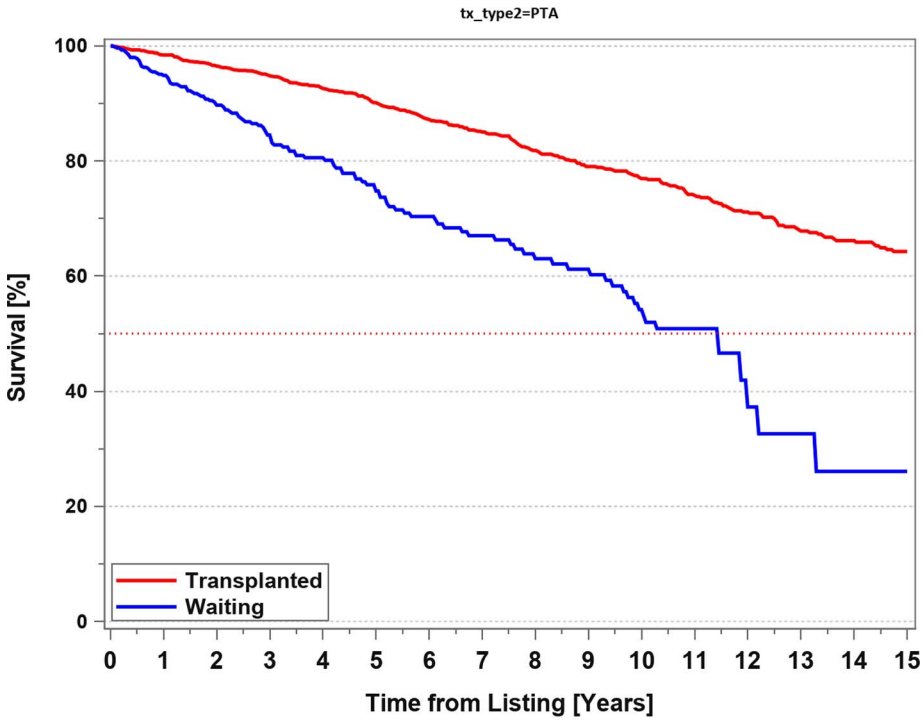

Figure 5. *PTA patient survival while on the waitlist vs transplanted between 1/1/2000 and 5/31/2021.*

Table 2. Life-years saved for all transplanted diabetic patients compared to patients still on the waitlist for a deceased donor primary transplant between 1/1/2000 and 5/31/2021

Category	N	Life-Years Saved	Life-Years/ Patient to Date
Total			
Waiting list	122,470	273,843	7.3
Transplant	88,581		
KTA			
Waiting list	115,886	126,441	6.6
Transplant	68,182		
PAK			
Waiting list	845	20,355	6.3
Transplant	2,662		
PTA			
Waiting list	583	10,159	6.4
Transplant	1,778		
SPK			
Waiting list	5,156	116,888	11.7
Transplant	15,959		

Table 3. Life-years saved for transplanted patients with type 1 diabetes mellitus compared to patients still on the waitlist for a deceased donor primary transplant between 1/1/2000 and 5/31/2021

Category	N	Life-Years saved	Life-Years/ Patient to Date
Total			
Waiting list	14,848	10,736	10.0
Transplant	25,584		
KTA			
Waiting list	9,431	31,180	8.2
Transplant	7,434		
PAK			
Waiting list	742	18,893	6.3
Transplant	2,449		
PTA			
Waiting list	542	9,660	6.6
Transplant	1,686		
SPK			
Waiting list	4,133	105,757	11.9
Transplant	14,015		

CONCLUSIONS

The life-saving nature and survival benefit of a kidney and/or pancreas transplant in all 4 diabetic recipient categories has repeatedly been shown in registry and single-center studies. These findings go along with a significant increase in life-expectancy after pancreas and/or kidney transplantation. Although the transplant procedures themselves are associated with a certain mortality risk, that risk exceeds the mortality risk on the waiting list only for the first few weeks or months after transplantation. The highest impact on outcome was found in the SPK category in which almost twice as many life-years were saved as in the KTA category. In general, dialysis status is a very influential risk factor for mortality: preemptive transplants before the development of end-stage renal disease increase life expectancy significantly. For that reason, the gain in survival time was less pronounced in the PAK category due to the previously restored kidney function which resulted in a lower waitlist mortality than in the SPK and KTA categories. Patients in the PTA category represent the healthiest population due to the lack of advanced secondary diabetic complications; hence, the surgical risk of the procedure itself has a higher impact on possible transplant mortality although the overall risk of death is minimal. Nevertheless, on average 6.4 life-years per patient were saved through a PTA transplant. Notably, transplant recipients with type 1 diabetes have a higher gain in life-years than recipients with type 2 diabetes; young transplant recipients (<30 years) have a lower gain than older recipients due to a significantly higher graft loss rate for immunological reasons.

Lastly, a combined 273,843 life-years saved over a 21-year time period resulted in approximately 13,000 life-years saved per year or adding another 7 years (on average) annually to almost 2000 diabetic pancreas and/or kidney recipients. The average number of life-years saved per patient (11.7 for SPK, 6.4 for PTA, 6.3 for PAK, and 6.6 for KTA recipients) contributes substantially to the fact that pancreas and/or kidney transplantation clearly prolongs and saves the lives of diabetic patients.

Insurance companies must not only be aware of the survival benefit of pancreas transplantation but also of the potential savings in health benefits.

REFERENCES

1. Gruessner RWG, Gruessner AC. Survival Benefit of Pancreas Transplantation. In: *Transplantation of the Pancreas*. 2nd Edition. Eds: Gruessner RWG, Gruessner AC. Cham: Springer International Publishing; 2023:961–968.
2. Port FK, Wolfe RA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. *JAMA*. 1993; 270:1339–1343.
3. Merion RM, Ashby VB, Wolfe RA, et al. Deceased--donor characteristics and the survival benefit of kidney transplantation. *JAMA*. 2005;294:2726–2733.
4. Ojo AO, Hanson JA, Meier-Kriesche HU, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol*. 2001; 12:589–597.
5. Schnitzler MA, Whiting JF, Brennan DC, et al. The life-years saved by a deceased organ donor. *Am J Transplant*. 2005;5:2289–2296.
6. Rana A, Gruessner A, Agopian VG, et al. Survival benefit of solid-organ transplant in the United States. *JAMA Surg*. 2015;150:252–259.
7. Meier-Kriesche HU, Ojo AO, Port FK, et al. Survival improvement among patients with end-stage renal disease: trends over time for transplant recipients and wait-listed patients. *J Am Soc Nephrol*. 2001;12: 1293–1296.
8. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. *N Engl J Med*. 1995;333:333–336.
9. Ojo AO, Meier-Kriesche HU, Hanson JA, et al. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. *Transplantation*. 2001;71:82–90.
10. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. *Lancet*. 2009;373:1808–1817.
11. Rayhill SC, D'Alessandro AM, Odorico JS, et al. Simultaneous pancreas-kidney transplantation and living related donor renal transplantation in patients with diabetes: is there a difference in survival? *Ann Surg*. 2000;231:417–423.
12. Smets YF, Westendorp RG, van der Pijl JW, et al. Effect of simultaneous pancreas-kidney transplantation on mortality of patients with type-1 diabetes mellitus and end-stage renal failure. *Lancet*. 1999;353: 1915–1919.
13. Esmeijer K, Hoogeveen E, van den Boog PJM, et al. Superior Long-term Survival for Simultaneous Pancreas-Kidney Transplantation as Renal Replacement Therapy: 30-Year Follow-up of a Nationwide Cohort. *Diabetes Care*. 2020;43:321–328.
14. Venstrom JM, McBride MA, Rother KI, et al. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. *JAMA*. 2003; 290:2817–2823.
15. Gruessner RW, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. *Am J Transplant*. 2004;4:2018–2026.
16. van Dellen D, Worthington J, Mitu-Pretorian OM, et al. Mortality in diabetes: pancreas transplantation is associated with significant survival benefit. *Nephrol Dial Transplant*. 2013;28:1315–1322.
17. Gruessner S, et al. Employment pattern after pancreas transplantation - Facts and Risk Factors - A Registry Analysis. *The Review of Diab Studies*. 2017;14(1).