PREEMPTIVE SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION HAS SURVIVAL BENEFIT TO PATIENTS

Running title: benefit of preemptive pancreas kidney transplant

AUTHORS: Enrique Montagud-Marrahi, MD[1,4], Elena Cuadrado-Payán, MD[1,4], Evelyn Hermida, MD[1,4], Judit Cacho, MD[1], David Cucchiari, MD, PhD[1,4], Ignacio Revuelta MD, PhD[1,4], Jimena del Risco-Zevallos, MD[1], Nuria Esforzado MD, PhD[1], Frederic Cofan MD, PhD[1], Federic Oppenheimer MD, PhD[1], Vicens Torregrosa, MD[1], Joana Ferrer MD, PhD[2], Antoni J Amor MD, PhD[3], Enric Esmatjes MD, PhD[3], Maria José Ramírez-Bajo MD, PhD[4], Mireia Musquera MD, PhD[5], Mathew Cooper, MD, PhD [6], Beatriu Bayes MD, PhD[1], Josep M Campistol MD, PhD[1,4], Fritz Diekmann MD, PhD[1,4*], Pedro Ventura-Aguiar MD, PhD[1,4*]

[1]Nephrology and Kidney Transplant Department. Hospital Clínic Barcelona, Spain.
[2]Hepatobiliopancreatic and Liver Transplant Department. Hospital Clínic Barcelona, Spain.
[3]Diabetes Unit. Endocrinology and Nutrition Department. Hospital Clínic Barcelona, Spain.
[4]Laboratori Experimental de Nefrologia I Trasplantament (LENIT), Fundació Clínic per a la Recerca Biomèdica (FCRB), Barcelona, Spain
[5]Urology Department, Hospital Clinic de Barcelona, Spain.
[6]Medstar Georgetown Transplant Institute, Washington, DC.

*Both authors contributed equally to the study design, analysis, and interpretation of results.

CORRESPONDING AUTHOR

Pedro Ventura-Aguiar,

pventura@clinic.cat

Nephrology and Kidney Transplant Department

Ext. +34962275444

Hospital Clínic de Barcelona

Carrer Villarroel 170, Barcelona, 08036, Spain

CO-CORRESPONDING AUTHOR

Fritz Diekmann,

fdiekman@clinic.cat

Nephrology and Kidney Transplant Department

Ext. +34962275444

Hospital Clínic de Barcelona

Carrer Villarroel 170, Barcelona, 08036, Spain

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ABSTRACT

Several organ allocation protocols give priority to waitlisted simultaneous kidney-pancreas (SPK) transplant recipients to mitigate the higher cardiovascular risk of patients with diabetes mellitus on dialysis. The available information regarding the impact of preemptive simultaneous kidney-pancreas transplantation on recipient and grafts outcomes is nonetheless controversial. To help resolve this, we explored the influence of preemptive simultaneous kidney-pancreas transplants on patient and graft survival through a retrospective analysis of the OPTN/UNOS database, encompassing 9690 simultaneous transplant recipients between 2000 and 2017. Statistical analysis was performed applying a propensity score analysis to minimize bias.

Of these patients 1796 (19%) were transplanted preemptively. At ten years recipient survival was significantly superior in the preemptive group when compared to the non-preemptive group (78.9% vs 71.8%). Dialysis at simultaneous kidney-pancreas transplantation was an independent significant risk for patient survival (hazard ratio 1.66 [95% confidence interval 1.32-2.09]), especially if the dialysis duration was 12 months or longer. Preemptive transplantation was also associated with significant superior kidney graft survival compared to those on dialysis (death-censored: 84.3% vs 75.4%, respectively; estimated half-life of 38.57 [38.33 –38.81] vs 22.35 [22.17 – 22.53] years, respectively). No differences were observed between both groups neither for pancreas graft survival nor for post-transplant surgical complications. Thus, our results sustain the relevance of early referral for pancreas transplantation and the importance of pancreas allocation priority in reducing patient mortality after simultaneous kidney-pancreas transplantation.

KEYWORDS: pancreas transplantation, kidney transplantation, simultaneous pancreas-kidney transplantation, preemptive transplantation, dialysis.

1. INTRODUCTION

Kidney transplantation is the treatment of choice for End-Stage Kidney Disease (ESKD), since it has been associated with improved patient survival and quality of life when compared to dialysis[1]. Preemptive kidney transplantation (i.e., kidney transplantation performed prior to initiation of dialysis) provides a higher and sustained benefit for both kidney graft and recipient when compared to non-preemptive kidney transplantation, thus becoming the optimal modality of kidney transplantation[2–4]. For patients with ESKD and diabetes mellitus (DM), despite the aetiology of ESKD, the mortality on dialysis is significantly higher to those without diabetes[5.] Simultaneous kidney-pancreas (SPK) is an established treatment alternative to patients with ESKD and DM that provides multiple benefits related to patient survival, an amelioration of micro- and macrovascular diabetes complications, and lower rates of cardiovascular events and mortality when compared to kidney transplantation alone[6–10]. Patient mortality on the waiting list for a SPK transplantation is up to 40% at 4 years, higher than the 15-20% reported in age similar kidney transplant recipients alone[11,12]. Previous studies have suggested thatin SPK a preemptive transplant approach is associated with a significant survival advantage, as well as fewer postoperative complications when compared to non-preemptive SPK, especially for patients with Type 1 Diabetes (T1D). Of relevance, improvement in dialysis treatments in the last 2 decades have led to a significant decrease in patient mortality and cardiovascular complications[13], which could translate into a reduction in the potential survival benefit of preemptive transplantation in patients with DM.

The benefits of a preemptive SPK in patients with ESKD and DM remains controversial, especially according to the data published in recent studies[14–19]. This information is crucial towards patient referral to transplant centers and organ allocation policies. Several national organ allocation policies try to mitigate this increase in cardiovascular risk through a priority towards patient in the kidney-pancreas transplant waitlist[20–23]. The aim of the present study was to evaluate the impact of preemptive SPK on long-term patient and grafts outcomes in a recent cohort of SPK recipients reported to the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) registry.

2. MATERIALS AND METHODS

2.1. Data Source

The present study used data from the OPTN/UNOS database, which includes data on donor, wait-listed candidates, and transplant recipients in the United States[24]. The study has been performed following the policy for using these data as established by the OPTN/UNOS institution.

2.2. Patient population

We conducted a longitudinal and retrospective study including recipients of a SPK from the OPTN/UNOS database between January 1st, 2000 and December 31st, 2017. We excluded recipients of multivisceral transplant other than SPK, of pancreas transplantation alone or pancreas after kidney transplant, whose donors' weight was < 30 kg[22], whose donors had a history of diabetes or in which this information was missing, and those with a history of diabetes other than Type 1 (T1D) or Type 2 (T2D) or those in which this information was missing. In total, 9690 pancreas recipients were included.

To explore the benefit derived from pancreas graft in preemptive SPK outcomes were compared with a matched preemptive kidney transplant alone (KTA) recipient cohort. To minimize selection bias, KTA only recipients with either T1D or T2d, between 18 and 55 years old (similar to the range observed in the SPK group) and with a BMI between 15 and 37 Kg/m^2 were included. In total, 12759 recipients were included.

2.3. Outcomes

Our primary outcomes were recipient survival and death-censored kidney or pancreas graft survival at 1, 5 and 10 years after transplantation. Our secondary outcomes were defined as any post-transplant surgical complication (as reported in the OPTN/UNOS database: local infection, anastomotic leak, pancreatitis, graft vessel thrombosis or bleeding) or pancreas or kidney graft rejection. To explore the benefit derived from pancreas graft in a preemptive context these outcomes were compared between preemptive SPK and preemptive kidney transplant alone (KTA) recipients (see the Supplementary Methods).

Patient were censored at the last day of follow-up or at death. Pancreas graft failure was defined as a permanent (>90 days) need for exogenous insulin[23], while kidney graft failure was defined as a permanent need for dialysis or re-transplantation.

2.4. Statistical analysis

Data are presented as mean (standard deviation, SD) for parametric variables and median (interquartile range [IQR]) for the non-parametric ones. The corresponding tests used were t-test, Mann-Whitney test and Chi-square as appropriated.

Inverse probability of treatment weighting (IPTW) was used to account for covariate imbalance between preemptive and non-preemptive transplant recipients. IPTW was estimated from a propensity score from a logistic regression model to undergo a preemptive SPK. The model included factors associated with the donor and either of the outcomes[25,26]: age, gender, body mass index (BMI), ethnicity (for both donor and recipient), donor serum amylase, donor serum lipase, donor after cardiac death (DCD), donor cardiac arrest after brain death, donor cause of death, donor history of smoking, hypertension and ischemic cardiopathy, vasoactive support at donation, Pancreas Donor Risk Index (PDRI), pancreas preservation time and solution, Kidney Donor Profile Index (KDPI), kidney cold ischemia time, recipient diabetes type, diabetes duration, recipient history of peripheral vascular disease, HLA mismatches, induction and maintenance immunosuppression, steroids withdrawal, pancreas functioning at 90 days post-transplant (pancreas early graft failure), and previous kidney and pancreas transplantation. The covariates included in the IPTW model for preemptive SPK and preemptive KTA comparison are detailed in the Supplementary Methods Section.

A stabilized weighting method was performed by multiplying the IPTW by the proportion of recipients of a preemptive and non-preemptive transplantation. Check for adequate balance of covariates after IPTW analyses was performed by calculation of standardized differences and an absolute difference greater than 0.1 represented a meaningful imbalance[27,28]. All subsequent analyses were performed on the weighted, covariate-balanced population. Kaplan-Meier was used to estimate patient and graft survival and compared using log-rank test. Binominal logistic regression was used to calculate odds ratio, and Cox proportional regression was performed to estimate patient and graft hazards. Half-life was defined as the time elapsed until 50% of the grafts have failed, and a linear regression analysis was performed to calculate half-life estimates[29].

In order to account for the potential dialysis lead time bias associated with recipient survival, dialysis duration (pre-transplant) was added to the beginning of follow-up time before transplantation, and a delayed entry survival model was performed so that patients did not enter the risk set until they received a transplant[30]. A similar approach was used to account for potential diabetes lead time, adding to the beginning of the follow-up of those patients with Type 1 Diabetes the mean difference of diabetes duration between Type 1 and Type 2 Diabetes recipients.

Statistical analysis was performed using IBM SPSS Statistics 26.0 (SPSS, Inc; Chicago, Illinois) software for MacOS. All tests were two-tailed and the significance level was defined as a P value <0.05. Graphs were performed using GraphPad Prism 8.4.0 (San Diego, California) software for MacOS.

3. RESULTS

3.1. Patient demographic characteristics

Among 9690 SPK recipients, 1796 (19%) were transplanted before initiation of dialysis (preemptive group), while 7894 (81%) were on dialysis at SPK procedure (non-preemptive group). For the overall cohort, the median time of follow-up was 5 [IQR 2 - 7] years. The mean age was slightly higher in the preemptive group (43.82 ± 8.92 vs 41.34 ± 8.64 years, respectively, P < 0.0001), which also were less frequently men (54% vs 64%, respectively, P < 0.0001) and more frequently Caucasian (83% vs 63%, respectively, P < 0.0001). The proportion of T2D patients was higher in the dialysis group (11% vs 5%, P < 0.0001), although diabetes duration (either for T1D or T2D) at SPK was longer in the preemptive one (30.01 ± 9.39 vs 26.12 ± 8.79 years, P < 0.0001). Non-preemptive SPK recipients exhibited a higher rate of peripheral vascular disease at transplantation (9% vs 7%, P = 0.003). The waiting list time for SPK was also longer in this group (7.50 [2.77 – 15.74] vs 6.12 [2.27 – 12.83] months, P < 0.0001). Table 1 summarizes baseline characteristics of the recipients.

Regarding the characteristics of the donors, smoking habit was slightly higher among donors from the preemptive group (11% vs 9%, P = 0.01) and were more frequently Caucasian (68% vs 65%, P = 0.03). There were no other significantly differences between both groups regarding donor characteristics (Table 1).

After IPTW procedure, no significant differences were observed between both groups neither for recipient nor for donor characteristics (Table S1).

3.2. Recipient survival

Patient survival at 1, 5 and 10 years after SPK was 97.6%, 91.7% and 78.9% in the preemptive group, respectively. For non-preemptive SPK recipients, survival was significantly lower, being 96.6%, 88.8% and 71.8% for the same time periods, respectively (Log Rank P < 0.0001) (Fig. 1A). After IPTW weighting, non-preemptive SPK was associated with an increased risk of recipient death when compared with the preemptive approach (HR 1.66 [95% CI 1.32 – 2.09], P < 0.0001) (Table 2).

To further explore the potential influence of dialysis duration before SPK in the dialysis group, this cohort was divided in two subgroups according to the time on dialysis before SPK (< 12 vs ≥ 12 months) and also compared with the preemptive group (Table S2). Recipients with a dialysis duration < 12 months exhibited higher survival rates when compared with their counterparts with ≥ 12 months on dialysis before SPK (97.5%, 91.0% and 74.7% vs 96.2%, 88.1% and 70.9% at 1, 5 and 10 years after SPK for the <

12 and ≥ 12 months group, respectively). Nevertheless, the preemptive group remained as the group with the highest survival rates (Log Rank $P < 0.0001$ for all comparisons) (Fig. 1B). After IPTW weighting, dialysis ≥ 12 months before SPK remained associated with an increased risk of recipient death (HR 1.78 [95% CI 1.42 – 2.24], $P < 0.0001$), whereas dialysis for < 12 months demonstrated a tendency but failed to reach statistical significance (HR 1.32 [95% CI 0.99 – 1.75], $P = 0.06$) (Table 2). Similar results were obtained when the analysis were performed adjusting by dialysis and diabetes lead time, as well as when the period in which the SPK was performed was considered (Table S3 and S4; Figure S2A and B).

When preemptive SPK recipients were compared to age-matched preemptive KTA recipients (Tables S5 and S6), patient survival at 1, 5 and 10 years was superior in the preemptive SPK group (Log Rank $P<0.001$)(Fig. S1A). Cox Regression analysis showed that preemptive KTA was associated with an increased risk of patient death ($P = 0.003$)(Table S7) despite donor type (Table S8).

3.3. Pancreas graft survival

Death-censored pancreas graft survival at 1, 5 and 10 years after transplantation was 92.2%, 86.0% and 80.5% for the preemptive group. These survival rates did not significantly differ from those from the nonpreemptive group (93.5%, 84.6% and 76.1% at 1, 5 and 10 years after transplantation, Log Rank $P = 0.57$)(Fig. 1C), nor were associated with a risk for pancreas graft failure (HR 1.09 [95% CI 0.93 – 1.29], $P = 0.30$) (Table 2).

The main cause of pancreas graft failure in the preemptive group was graft thrombosis (41%), while in the non-preemptive one was pancreas rejection (36%). Causes of pancreas graft loss did not significantly differ between both groups (P = 0.07) (Table 3).

Death-censored pancreas graft survival was also similar when taking into account dialysis duration before transplantation (93.8%, 84.6% and 76.4% vs 93.4%, 84.7% and 75.9% at 1, 5 and 10 years after transplantation for the < 12 and ≥ 12 months dialysis groups, respectively; Log Rank P = 0.85 for all comparisons)(Fig. 1D). After IPTW weighting, neither dialysis < 12 months before SPK (HR 1.05 [95% CI 0.85 – 1.30], P = 0.64) nor dialysis for ≥ 12 months (HR 1.11 [95% CI 0.93 – 1.31], P = 0.24) were associated with an increased risk of pancreas graft loss (Table 2). Similar results were observed when the period in which the SPK was performed was split into two major eras: 2000-2009 or 2010-2017(Table S4 and Figure S2C and D).

3.4. Kidney graft survival

Death-censored kidney graft survival was significantly higher in the preemptive group, with kidney survival rates of 97.8%, 91.4% and 84.3% at 1, 5 and 10 years after SPK, respectively, compared to 97.63%, 88.1% and 75.4% for dialysis group in the same time periods (Log Rank P < 0.0001) (Fig. 1E). Kidney graft half-life estimates were higher for the preemptive group (38.57 [95% CI 38.33 – 38.81] vs 22.35 [95% CI 22.17 – 22.53] years for the preemptive and non-preemptive group, respectively). After IPTW weighting, non-preemptive SPK was associated with an increased risk of kidney graft loss (HR 1.46 [95% CI 1.18 – 1.81], P = 0.001) (Table 2).

For both groups, the main cause of kidney graft failure was kidney rejection (50% and 57% for the preemptive and dialysis group, respectively), without significant statistical differences between both groups (Table 3).

When considering time on dialysis before SPK, dialysis recipients with ≥ 12 months on dialysis before SPK exhibited the lowest kidney survival rates when compared to those recipients on dialysis for < 12 months and with the preemptive groups (98.4%, 90.2% and 77.6% for the < 12 months vs 97.4%, 87.3% and 74.3% for ≥ 12 months dialysis at 1, 5 and 10 years after transplantation, respectively; Log Rank P < 0.0001 for all comparisons)(Fig. 1F). After IPTW weighting, dialysis ≥ 12 months before SPK was associated with an increased risk of kidney graft failure (HR 1.53 [95% CI 1.23 – 1.91], P < 0.0001), but no association was noted for dialysis for <12 months (P = 0.13) (Table 2).

When preemptive SPK recipients were compared to age-matched preemptive KTA recipients, death-censored kidney graft survival was comparable between both groups (P=0.55) (Fig.S1B). In the IPTW adjusted Cox Regression analysis, preemptive KTA was significantly associated with an increased risk of kidney graft loss compared to preemptive SPK (P=0.002) (Table S7). LDKT was nonetheless associated with a lower risk of kidney graft failure compared to preemptive SPK (P=0.01)(Table S8).

Finally, when analysed separately for T1D and T2D patients, recipient and graft survival was significantly higher for the preemptive group compared to the non-preemptive one in patients with T1D. Conversely, preemptive SPK in T2D patients did not improve recipient nor kidney graft survivals. Pancreas graft survival was comparable between both groups (Tables S9 and S10, and Figure S3). Similar results were observed when the period in which the SPK was performed was considered (Table S4 and Figure S2E and F).

3.4. Post-transplant complications

The most frequent post-transplant complication in both groups was pancreas rejection, which was slightly but significantly more frequent in non-preemptive SPK recipients (11% vs 9% for preemptive recipients, P = 0.046), followed by kidney graft rejection (8% vs 7% for non-preemptive and preemptive SPK recipients, respectively, P = 0.18) (Table 4). No differences were observed between groups regarding pancreas graft rejection (P = 0.07) nor kidney graft rejection (P = 0.27)(Table S11).

No significant differences were observed between both groups for surgical complications (Table 4). Specifically, preemptive SPK was not associated with a higher rate for graft thrombosis nor bleeding when compared to the non-preemptive approach.

4. DISCUSSION

In this study we have analysed short- and long-term recipient, pancreas and kidney graft outcomes in recipients of a SPK who are transplanted in a preemptive status, comparing them with those already on dialysis at the time of transplantation. In a cohort of 9690 SPK recipients, preemptive SPK was associated with a reduction in the risk of recipient death or kidney graft failure up to 66% and 46% when compared with recipients transplanted who had already initiated dialysis. Furthermore, the longer the time on dialysis the worse recipient and kidney graft survivals. Finally, preemptive SPK recipients exhibited a survival benefit when compared to an age-matched cohort of patients with diabetes who received a preemptive KTA. Overall, our findings suggest that preemptive SPK is associated with a significant survival advantage for patients with diabetes and ESKD, thus reinforcing the need for an early referral of these patients to be evaluated as potential SPK recipients.

Kidney transplantation has demonstrated to offer the best patient survival rates when compared to dialysis, thus being the optimal treatment for patients with ESKD[1]. Among the different kidney transplant modalities, preemptive kidney transplantation is associated with better patient and kidney graft survival compared to kidney transplantation performed after dialysis initiation, thus being the preferred transplantation strategy[2–4].

SPK constitutes an established treatment for patients with ESKD and diabetes, since it provides a significant reduction of cardiovascular risk and higher patient survival when compared with kidney transplantation alone[6–10]. Moreover, based on results from previous studies, preemptive SPK seems to also be associated with better results compared to a non-preemptive strategy[14,19]. Despite the potential benefits provided by a preemptive SPK, the percentage of patients with ESKD and DM who are transplanted in a pre-dialysis status remains significantly low[6,14,15]. This scenario has not substantially changed during the last years despite increasing evidence in favour of preemptive SPK, mostly because patients are still referred to SPK pre-transplant evaluation specialized units when kidney disease is severely advanced and dialysis onset is imminent[6,14,15]. Although waiting time for an SPK has decreased in a most recent era [26,27], the historical longer waiting time for an SPK than for those receiving a pancreas after kidney transplantation may have further contributed to the late referral.

Some studies have previously assessed the potential benefits associated with preemptive SPK[14–19,31]. Israni et al.[19] retrospectively explored the influence of preemptive SPK on kidney graft survival in a large cohort of SPK recipients and observed that preemptive SPK (vs non-preemptive) was associated with a significantly lower rate of kidney graft failure (20% decrease). Similarly, Becker et al.[32] reported that preemptive SPK was associated with lower recipient mortality (50% decrease) and kidney graft loss (13% decrease) in patients with T1D. However, a constant observation in these previous studies is that preemptive SPK seems not significantly influence pancreas graft outcomes. These results are in line with that described here, although in our study the benefit from a preemptive SPK was substantially higher for both recipient and kidney graft. These discrepancies might be justified by the technical and immunological improvements that SPK has recently experienced. In contrast to our results, Parajuli et al[15] recently reported that preemptive SPK presented a tendency towards improved recipient and kidney graft outcomes, but failed to reach statistical significance. The discrepancy in the results may rely on the smaller single center cohort included in that study.

Regarding post-transplant complications, we did not find significantly differences between both study groups, as well as preemptive SPK seemed not to be associated with a higher risk of post-transplant complications (such as pancreas graft thrombosis). These results contrast with those described by Grochowiecki et al[16], although this study only included 112 SPK recipients (25 preemptive) and postoperative complications were classified and analysed according to the Clavien Dindo classification, a more detailed classification which was not available for comparison in the OPTN/UNOS database.

Another important issue we raised here is the influence of time on dialysis among those SPK recipients transplanted non-preemptively. In kidney transplantation, long-term dialysis demonstrated to negatively affect transplant outcomes and it has been associated with an increased risk of recipient death and kidney graft failure after transplantation[33–35]. Dong et al[14] assessed the influence of pre-SPK dialysis time on recipient, kidney and pancreas graft outcomes in a cohort of 6887 SPK recipients. They reported that a dialysis duration >2years before SPK significantly increased the risk for recipient and kidney graft survival, whereas shorter periods (0-2 years) did not . These results are aligned with the ones observed in the study herein presented in which dialysis >12 months was an independent risk factor for recipient death and kidney graft failure.

Improvement in dialysis and diabetes treatment have led to an overall improvement in patient survival in the last decades. Of relevance, and despite these improvements, preemptive SPK still entailed a benefit over non-preemptive SPK in patient and kidney graft survival in the more recent era (2010-2017).

In an attempt to provide insight on the relevance of the pancreas graft on the reported improved patient outcomes in preemptive SPK transplantation, we performed a comparison to an age-matched cohort of patients with T1D and T2d who received a preemptive KTA. While taking into consideration there is a potential positive patient selection bias for SPK recipients, we observed that preemptive SPK was associated with a 34% lower risk of recipient death when compared to preemptive KTA. Most importantly, the associated benefits from a preemptive SPK on patient survival persisted when compared to preemptive LDKT (Table S6). These results are in accordance with those already described in previous studies for non-preemptive SPK[7,9,36,37]. This survival advantage is probably explained by the important cardiovascular benefit that SPK entails, since this transplant option has demonstrated to significantly attenuate the progression of diabetes complications and reduce cardiovascular risk and cardiovascular death in patients with diabetes[6,9,38–40]. Our results reinforce the sustained benefits associated with preemptive SPK over KTA, even when such an ideal situation as preemptive LDKT is considered[7–11].

Our study has some limitations. Firstly, it is a registry study, in which data collection may have led to misclassification, measurement error, and missing data. Secondly, and inherent to using registry data, the information about important recipient and donor characteristics, such as baseline cardiovascular profile, comorbidity, medical history, recipient cause of death and pharmacological treatment is limited. Finally, and inherent to studies which compare SPK vs KTA recipients, there is an important selection bias, since patients with higher comorbidity and poor status are considered to be high risk patients and usually are discarded for SPK, thus only being accepted for KTA. Although here we have performed a IPTW adjustment through a propensity score analysis, residual confounding may remain.

As closing remarks, herein we report that preemptive or early (<12months on dialysis) SPK transplant significantly improves recipient and kidney graft survival after transplantation. This finding reinforces the experts' recommendations in which patients with ESKD and diabetes mellitus who are eligible to receive a SPK should be referred early to pre-transplant evaluation to enable an inclusion and eventually access to transplant prior to the initiation of dialysis[41].

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by Kidney International.

DATA AVAILABILITY STATEMENT

The data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

FIGURE LEGENDS

Figure 1. Recipient, pancreas and kidney graft survival according to pre-SPK dialysis status. A, Recipient survival according to pre-transplant dialysis status. B, Recipient survival according to pre-transplant dialysis status and time on dialysis. C, Death-censored pancreas graft survival according to pre-transplant dialysis status. D, Death-censored pancreas graft survival according to pre-transplant dialysis status and time on dialysis. E, Death-censored kidney graft survival according to pre-transplant dialysis status. F, Death-censored kidney graft survival according to pre-transplant dialysis status and time on dialysis. SPK, Simultaneous Pancreas-Kidney Transplantation.

SUPPLEMENTARY MATERIAL

- Supplementary Methods
- Table S1. Standardized differences before and after IPTW adjustment for preemptive SPK and non-preemptive SPK comparison.
- Table S2. Recipient and donor baseline characteristics according to time on dialysis
- Table S3. Hazard ratios for recipient, pancreas and kidney graft survival adjusted by dialysis lead time and diabetes lead time.
- Table S4. IPTW weighted hazard ratios for recipient survival, death-censored pancreas graft survival and death-censored kidney graft survival according for the periods 2000 – 2009 and 2010 – 2017.
- Table S5. Recipient and donor baseline characteristics for preemptive KTA and preemptive SPK.
- Table S6. Standardized differences before and after IPTW adjustment for preemptive SPK and preemptive KTA recipients
- Table S7. Unadjusted and IPTW weighted hazard ratios for recipient survival and death-censored kidney graft survival
- Table S8. Unadjusted and IPTW weighted hazard ratios for recipient survival and death-censored kidney graft survival according to donor type.
- Table S9. Hazard ratios for recipient survival, death-censored pancreas graft survival and death-censored kidney graft survival for patients with T1D and T2D.
- Table S10. Hazard ratios for recipient survival for patients with T1D and T2D adjusted by diabetes lead time.
- Table S11. IPTW adjusted logistic regression for any post-transplant complication and graft rejection for preemptive and non-preemptive SPK.

- Figure S1. Recipient and kidney graft survival according to transplant modality and type of diabetes. A, Recipient survival according to transplant modality. B, Death censored kidney graft survival according to transplant modality. SPK, Simultaneous Pancreas-Kidney Transplantation; KTA, Kidney Transplantation Alone.
- Figure S2. Recipient, pancreas and kidney graft survival according to pre-SPK dialysis status for two periods (2000-2009 and 2010-2017). A, Recipient survival according to pre-transplant dialysis status for the period 2000-2009. B, Recipient survival according to pre-transplant dialysis status for the period 2010-2017. C, Death-censored pancreas graft survival according to pre-transplant dialysis status for the period 2000-2009. D, Death-censored pancreas graft survival according to pre-transplant dialysis status for the period 2010-2017. E, Death-censored kidney graft survival according to pre-transplant dialysis status for the period 2000-2009. F, Death-censored kidney graft survival according to pre-transplant dialysis status for the period 2010-2017. SPK, Simultaneous Pancreas-Kidney Transplantation.
- Figure S3. Recipient, pancreas and kidney graft survival according to pre-SPK dialysis status for T1D and T2D patients. A, Recipient survival according to pre-transplant dialysis status for T1D recipients. B, Recipient survival according to pre-transplant dialysis status for T2D recipients. C, Death-censored pancreas graft survival according to pre-transplant dialysis status for T1D recipients. D, Death-censored pancreas graft survival according to pre-transplant dialysis status for T2D recipients. E, Death-censored kidney graft survival according to pre-transplant dialysis status for T1D recipients. F, Death-censored kidney graft survival according to pre-transplant dialysis status for T2D recipients. SPK,

Simultaneous Pancreas-Kidney Transplantation. T1D, Type 1 Diabetes; T2D, Type 2 Diabetes.

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TABLES

Table 1 - Recipient and donor baseline characteristics

	Preemptive SPK (n = 1796)	Non-preemptive SPK (n = 7894)	P
Donor			
Age (years)	25.47 ± 9.37	25.06 ± 9.09	0.09
Gender (male)	1233 (69)	5516 (70)	0.31
Ethnicity			0.03
Caucasian/Other	1216 (68)	5134 (65)	
African American	331 (18)	1456 (18)	
Hispanic	214 (12)	1150 (15)	
Asian	35 (2)	154 (2)	
BMI (kg/m^2)	24.08 ± 3.97	24.08 ± 3.89	0.99
Smoking habit (yes)	192 (11)	679 (9)	0.01
Hypertension (yes)	84 (5)	400 (5)	0.49
Ischemic Heart Disease (yes)	9 (1)	48 (1)	0.59
Vasoactive support at donation (yes)	933 (52)	3997 (51)	0.32
Kidney CIT (h)	11.16 ± 5.55	11.27 ± 5.27	0.44
KDPI	0.21 ± 0.16	0.20 ± 0.17	0.28
Pancreas preservation time (h)	11.41 ± 5.57	11.43 ± 5.24	0.89
PDRI	1.10 ± 0.38	1.09 ± 0.35	0.21
SCr at donation (mg/dL)	1.00 ± 0.66	0.99 ± 0.60	0.31
Serum Amylase (U/L)	66 [35 - 125]	62 [34 - 126]	0.38
Serum Lipase (U/L)	22 [13 - 59]	24 [14 - 63]	0.09
Serum AST (U/L)	46 [29 - 79]	46 [29 - 81]	0.89
Serum ALT (U/L)	34 [22 - 61]	34 [21 - 62]	0.62
Serum total bilirubin (mg/dL)	0.8 [0.5 – 1.2]	0.8 [0.5 – 1.2]	0.93
BUN (mg/dL)	14.01 ± 9.89	14.05 ± 8.41	0.84
Cause of death			0.28
Anoxia	342 (19)	1528 (19)	
Cerebrovascular Event	272 (15)	1131 (15)	
Head Trauma	1128 (63)	5059 (64)	
Other	54 (3)	176 (2)	
Donor after cardiac death (yes)	50 (3)	228 (3)	0.81
Cardiac arrest after brain death (yes)	122 (7)	540 (7)	0.94
Recipient			
Age at PT (years)	43.82 ± 8.92	41.34 ± 8.64	< 0.0001
Gender (male)	977 (54)	5079 (64)	< 0.0001
Ethnicity			< 0.0001
Caucasian/Other	1482 (83)	4877 (63)	
African American	176 (9)	51 (22)	
Hispanic	110 (6)	1020 (13)	
Asian	28 (2)	156 (2)	
BMI (kg/m^2)	25.54 ± 3.84	25.18 ± 3.84	< 0.0001
Diabetes Type			< 0.0001
Type 1	1702 (95)	7052 (89)	
Type 2	94 (5)	842 (11)	
Diabetes Duration (years)	30.01 ± 9.39	26.12 ± 8.79	< 0.0001
Dialysis Duration (years)			
> 12 months	-	2004 (25)	
≤ 12 months	-	5890 (75)	
Peripheral vascular disease (yes)	118 (7)	691 (9)	0.003
WL time for SPK (months)	6.12 [2.27 – 12.83]	7.50 [2.77 – 15.74]	< 0.0001
Previous KT (yes)	90 (5)	266 (3)	0.001
Previous PT (yes)	48 (3)	118 (2)	0.001
Pancreas drainage			0.14
Enteric	1622 (90)	7005 (89)	
Bladder	124 (7)	617 (8)	
Other	50 (3)	272 (3)	
cPRA pretransplant (%)	7.31 ± 19.45	9.39 ± 22.22	0.03

Total HLA Mismatches	4.52 ± 1.16	4.57 ± 1.16	0.003
Induction Immunosuppression			< 0.0001
Thymoglobulin	1082 (60)	5056 (64)	
Basiliximab/Daclizumab	191 (11)	634 (8)	
Alemtuzumab	263 (14)	1015 (13)	
Other	260 (15)	1189 (15)	
Maintenance Immunosuppression			0.004
TAC + MMF + Steroids	1077 (60)	5063 (64)	
TAC + MMF	507 (28)	1904 (24)	
TAC + mTORi + Steroids	22 (1)	90 (1)	
TAC + mTORi	175 (10)	741 (10)	
CsA + MMF + Steroids	12 (0.8)	61 (0.6)	
Other combination	3 (0.2)	35 (0.4)	
Steroids Withdrawal (yes)	237 (13)	1058 (13)	0.82

Data are mean ± SD, median [IQR] or n (%), unless otherwise specified. SPK, Simultaneous Pancreas-Kidney, BMI, Body Mass Index; CIT, Cold Ischemia Time; KDPI, Kidney Donor Profile Index; PDRI, Pancreas Donor Risk Index; SCr, Serum Creatinine; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BUN, Blood Urea Nitrogen: PT, Pancreas Transplantation;; WL, Waiting List; KT, Kidney Transplantation; TAC, Tacrolimus; MMF, Mycophenolate; mTORi, mTOR inhibitors; CsA, Cyclosporine.

Table 2 – IPTW weighted hazard ratios for recipient survival, death-censored pancreas graft survival and death-censored kidney graft survival

		95% CI		
Variable	HR	LL	UL	P
Recipient survival				
Dialysis before SPK (yes)	1.66	1.32	2.09	< 0.0001
Preemptive	1.00			
< 12 months	1.32	0.99	1.75	0.06
≥ 12 months	1.78	1.42	2.24	< 0.0001
DC Pancreas graft survival				
Dialysis before SPK (yes)	1.09	0.93	1.29	0.30
Preemptive	1.00			
< 12 months	1.05	0.85	1.30	0.64
≥ 12 months	1.11	0.93	1.31	0.24
DC Kidney Graft Survival				
Dialysis before SPK (yes)	1.46	1.18	1.81	0.001
Preemptive	1.00			
< 12 months	1.24	0.94	1.62	0.13
≥ 12 months	1.53	1.23	1.91	< 0.0001

DC, Death-censored; SPK, Simultaneous Pancreas-Kidney transplantation.

Table 3 - Causes of pancreas and kidney graft loss

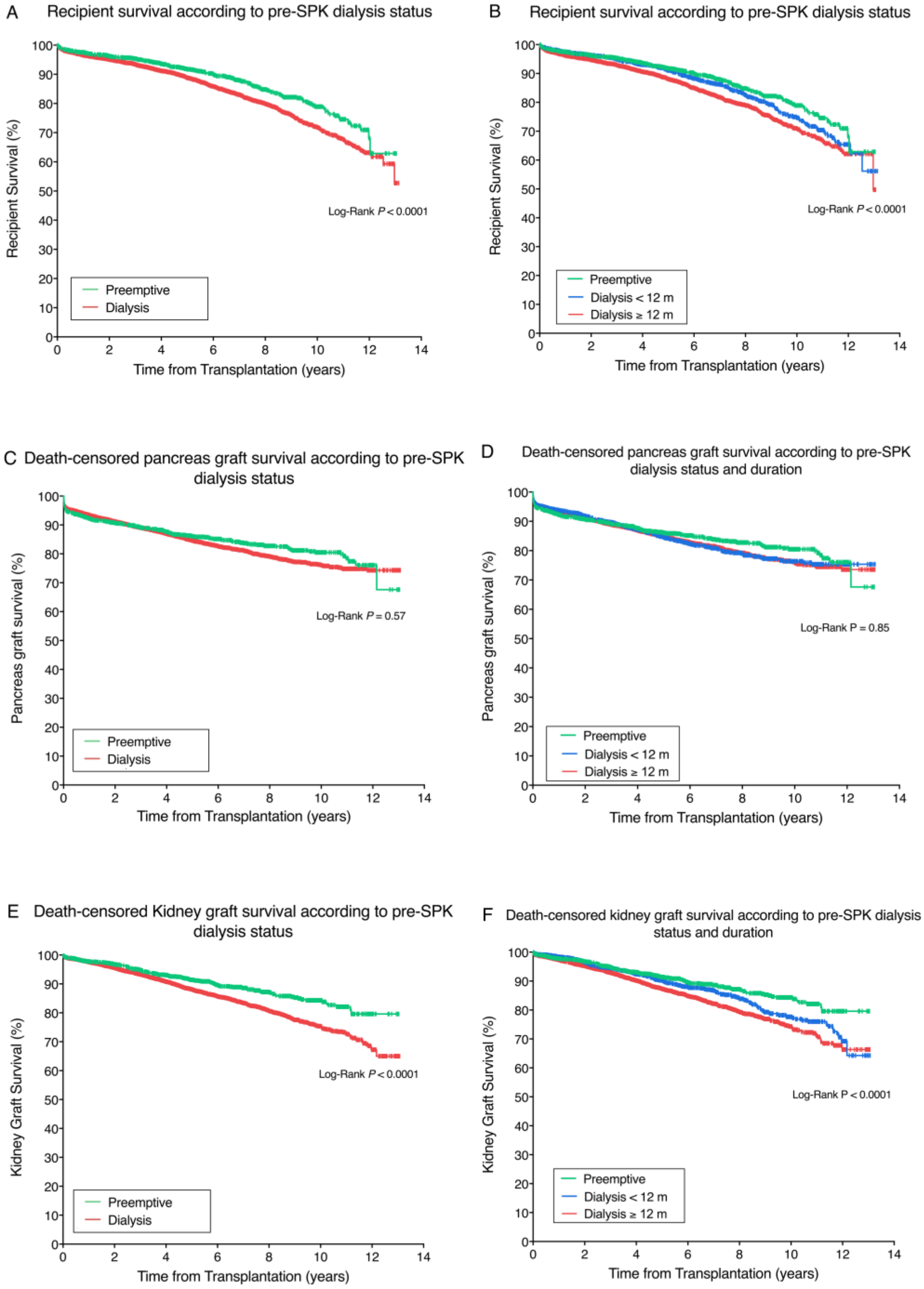
	Preemptive SPK	Non-preemptive SPK	P
Pancreas graft			
Death with functioning graft	129	739	
Failed grafts (n)	301	1301	
Primary non-function	9 (3)	50 (4)	0.07
Local infection	12 (4)	45 (4)	
Anastomotic leak	5 (2)	34 (3)	
Pancreatitis	8 (3)	44 (3)	
Graft Vessel Thrombosis	122 (41)	388 (30)	
Bleeding	4 (1)	21 (2)	
Pancreas rejection	93 (31)	474 (36)	
Acute	50 (17)	241 (19)	
Chronic	43 (14)	233 (17)	
Other/Unknown	48 (15)	245 (18)	
Kidney Graft			
Death with functioning graft	134	607	
Failed grafts (n)	173	996	
Primary non-function	3 (2)	30 (3)	0.15
Kidney rejection	87 (50)	568 (57)	
Thrombosis	21 (12)	73 (7)	
Infection	6 (4)	28 (3)	
Surgical complication	1 (1)	6 (1)	
Recurrence of kidney disease	7 (4)	22 (2)	
BK virus nephropathy	11 (6)	34 (4)	
Other/Unknown	37 (21)	233 (23)	

Data are n (%), unless otherwise specified. SPK, Simultaneous Pancreas-Kidney transplant.

Table 4 – Post-transplant complications for preemptive and non-preemptive recipients.

	Preemptive SPK (n = 1796)	Non-preemptive SPK (n = 7894)	P
Local infection	52 (3)	263 (3)	0.38
Anastomotic leak	28 (2)	140 (2)	0.62
Pancreatitis	45 (3)	198 (3)	0.99
Graft Vessel Thrombosis	15 (1)	57 (1)	0.62
Bleeding	9 (0.5)	40 (0.5)	0.98
Pancreas rejection	167 (9)	861 (11)	0.046
Acute	116 (6)	580 (7)	
Chronic	51 (3)	281 (4)	
Kidney rejection	122 (7)	609 (8)	0.18
Other	19 (1)	122 (2)	0.12

Figure 1


A
Recipient survival according to pre-SPK dialysis status
Recipient Survival (%)
Time from Transplantation (years)
Log-Rank P < 0.0001
Preemptive
Dialysis
B
Recipient survival according to pre-SPK dialysis status
Recipient Survival (%)
Time from Transplantation (years)
Log-Rank P < 0.0001
Preemptive
Dialysis < 12 m
Dialysis ≥ 12 m
C
Death-censored pancreas graft survival according to pre-SPK dialysis status
Pancreas graft survival (%)
Time from Transplantation (years)
Log-Rank P = 0.57
Preemptive
Dialysis
D
Death-censored pancreas graft survival according to pre-SPK dialysis status and duration
Pancreas graft survival (%)
Time from Transplantation (years)
Log-Rank P = 0.85
Preemptive
Dialysis < 12 m
Dialysis ≥ 12 m
E
Death-censored Kidney graft survival according to pre-SPK dialysis status
Kidney Graft Survival (%)
Time from Transplantation (years)
Log-Rank P < 0.0001
Preemptive
Dialysis
F
Death-censored kidney graft survival according to pre-SPK dialysis status and duration
Kidney Graft Survival (%)
Time from Transplantation (years)
Log-Rank P < 0.0001
Preemptive
Dialysis < 12 m
Dialysis ≥ 12 m

ONLINE-ONLY SUPPLEMENTAL MATERIAL

1. Supplementary Methods

1.1. Included covariates for IPTW adjustment for preemptive SPK and KTA comparison.

For the comparison between preemptive SPK and preemptive KTA, the model included: age, gender, BMI (for both donor and recipient), donor history of smoking and hypertension, kidney cold ischemia time, recipient ethnicity, recipient diabetes type, diabetes duration at transplantation, recipient history of peripheral vascular disease, HLA mismatches and induction immunosuppression.

Table S1 – Standardized differences before and after IPTW adjustment for preemptive SPK and non-preemptive SPK comparison.

	Before IPTW adjustment	After IPTW adjustment
Donor		
Age (years)	-0.044	-0.021
Gender (male)	-0.018	0.001
Ethnicity		
Caucasian/Other	-0.046	-0.009
African American	0.001	-0.007
Hispanic	0.063	0.018
Asian	0.001	0.006
BMI (kg/m^2)	0.001	-0.014
Smoking habit (yes)	-0.055	0.001
Hypertension (yes)	0.001	-0.040
Ischemic Heart Disease (yes)	0.001	0.001
Vasoactive support at donation (yes)	-0.016	0.001
Kidney CIT (h)	0.02	-0,002
KDPI	-0.029	-0.023
Pancreas preservation time (h)	0.004	-0.019
PDRI	-0.033	-0.031
SCr at donation (mg/dL)	-0.026	-0.001
Serum Amylase (U/L)	0.005	0.024
Serum Lipase (U/L)	0.014	0.027
Serum AST (U/L)	-0.005	0.004
Serum ALT (U/L)	0.016	0.007
Serum total bilirubin (mg/dL)	-0.025	0.013
BUN (mg/dL)	0.005	-0.004
Cause of death		
Anoxia	0.007	-0.012
Cerebrovascular Event	-0.019	-0.010
Head Trauma	0.022	0.026
Other	-0.041	-0.025
Donor after cardiac death (yes)	0.001	0.001
Cardiac arrest after brain death (yes)	0.001	0.001
Age at PT (years)	-0.282	-0.001
Gender (male)	-0.168	-0.017
Ethnicity		
Caucasian/Other	-0.352	-0.078
African American	0.263	0.086
Hispanic	0.181	0.030
Asian	0.026	-0.005
BMI (kg/m^2)	-0.095	-0.001
Diabetes Type	0.001	0.052
Diabetes Vintage (years)	-0.428	-0.007
Peripheral vascular disease (yes)	0.059	0.001
Previous KT (yes)	-0.087	0.001
Previous PT (yes)	-0.128	0.001
cPRA pretransplant (%)	0.100	-0.030
Total HLA Mismatches	0.043	-0.018
Induction Immunosuppression		
Thymoglobulin	0.064	0.032
Basiliximab/Daclizumab	-0.075	-0.058
Alemtuzumab	-0.043	-0.026
Other	0.013	0.035
Maintenance Immunosuppression		
TAC + MMF + Steroids	0.068	0.035
TAC + MMF	-0.613	-0.018
TAC + mTORi + Steroids	0.001	0.001
TAC + mTORi	-0.072	-0.059
CsA + MMF + Steroids	0.001	0.001
Other combination	0,037	0.046
Steroids Withdrawal (yes)	0,001	0.001

Pancreas Early Graft Failure (yes)	-0.031	0.033

SPK, Simultaneous Pancreas-Kidney, BMI, Body Mass Index; CIT, Cold Ischemia Time; KDPI, Kidney Donor Profile Index; PDRI, Pancreas Donor Risk Index; SCr, Serum Creatinine; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BUN, Blood Urea Nitrogen: PT, Pancreas Transplantation; WL, Waiting List; KT, Kidney Transplantation; TAC, Tacrolimus; MMF, Mycophenolate; mTORi, mTOR inhibitors; CsA, Cyclosporine.

Table S2 - Recipient and donor baseline characteristics according to time on dialysis

	Preemptive SPK or Dialysis < 12 m (n = 3800)	Dialysis ≥ 12 m (n = 5890)	P
Donor			
Age (years)	25.44 ± 9.44	24.94 ± 8.94	0.01
Gender (male)	2607 (69)	4142 (70)	0.07
Ethnicity			< 0.001
Caucasian/Other	2619 (68)	3731 (63)	
African American	669 (18)	1118 (19)	
Hispanic	440 (12)	924 (16)	
Asian	72 (2)	117 (2)	
BMI (kg/m^2)	24.10 ± 4.01	24.06 ± 3.83	0.62
Smoking habit (yes)	391 (10)	480 (8)	< 0.001
Hypertension (yes)	206 (5)	278 (5)	0.13
Ischemic Heart Disease (yes)	23 (1)	34 (1)	0.89
Vasoactive support at donation (yes)	2013 (53)	2917 (50)	< 0.001
Kidney CIT (h)	11.23 ± 5.44	11.26 ± 5.25	0.87
KDPI	0.21 ± 0.17	0.20 ± 0.17	0.06
Pancreas preservation time (h)	11.35 ± 5.24	11.46 ± 5.35	0.46
PDRI	1.10 ± 0.38	1.08 ± 0.35	0.02
SCr at donation (mg/dL)	0.99 ± 0.64	0.99 ± 0.59	0.56
Serum Amylase (U/L)	63 [34 - 124]	63 [34 - 127]	0.45
Serum Lipase (U/L)	23 [13 - 62]	23 [13 - 62]	0.84
Serum AST (U/L)	46 [29 - 82]	46 [29 - 80]	0.11
Serum ALT (U/L)	34 [21 - 62]	34 [21 - 61]	0.73
Serum total bilirubin (mg/dL)	0.8 [0.5 – 1.2]	0.8 [0.5 – 1.2]	0.59
BUN (mg/dL)	13.76 ± 8.79	14.23 ± 8.64	0.01
Cause of death			0.99
Anoxia	740 (19)	1130 (19)	
Cerebrovascular Event	550 (15)	853 (15)	
Head Trauma	2420 (64)	3767 (64)	
Other	90 (2)	140 (2)	
Donor after cardiac death (yes)	127 (3)	151 (3)	0.80
Cardiac arrest after brain death (yes)	254 (7)	408 (7)	0.65
Recipient			
Age at PT (years)	42.40 ± 8.98	41.41 ± 8.57	< 0.0001
Gender (male)	2222 (59)	3834 (65)	< 0.0001
Ethnicity			< 0.0001
Caucasian/Other	2977 (77)	3482 (59)	
African American	476 (13)	1441 (25)	
Hispanic	289 (8)	841 (14)	
Asian	58 (2)	126 (2)	
BMI (kg/m^2)	25.52 ± 3.84	25.23 ± 3.87	< 0.0001
Diabetes Type			< 0.0001
Type 1	3541 (93)	5213 (89)	
Type 2	259 (7)	677 (12)	
Diabetes Duration (years)	28.08 ± 9.39	26.05 ± 8.70	< 0.0001
Peripheral vascular disease (yes)	266 (7)	543 (9)	< 0.0001
WL time for SPK (months)	4.78 [1.90 – 10.19]	9.50 [3.67 – 18.40]	< 0.0001
Previous KT (yes)	148 (4)	208 (2)	0.38
Previous PT (yes)	64 (2)	101 (2)	0.94
Pancreas drainage			0.37
Enteric	3387 (89)	5240 (89)	
Bladder	298 (8)	443 (8)	
Other	115 (3)	207 (3)	
cPRA pretransplant (%)	4.30 ± 14.17	6.00 ± 17.36	0.02
Total HLA Mismatches	4.55 ± 1.14	4.57 ± 1.17	0.42
Induction Immunosuppression			< 0.0001
Thymoglobulin	2289 (60)	3849 (65)	
Basiliximab/Daclizumab	403 (11)	422 (7)	

Alemtuzumab	553 (15)	725 (13)	
Other	555 (14)	894 (15)	
Maintenance Immunosuppression			0.12
TAC + MMF + Steroids	2374 (63)	3766 (64)	
TAC + MMF	962 (25)	1449 (25)	
TAC + mTORi + Steroids	41 (1)	71 (1)	
TAC + mTORi	386 (10)	530 (9)	
CsA + MMF + Steroids	28 (0.7)	45 (0.8)	
Other combination	9 (0.3)	29 (0.2)	
Steroids Withdrawal (yes)	541 (14)	5136 (13)	0.04

Data are mean ± SD, median [IQR] or n (%), unless otherwise specified. SPK, Simultaneous Pancreas-Kidney, BMI, Body Mass Index; CIT, Cold Ischemia Time; KDPI, Kidney Donor Profile Index; PDRI, Pancreas Donor Risk Index; SCr, Serum Creatinine; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BUN, Blood Urea Nitrogen: PT, Pancreas Transplantation;; WL, Waiting List; KT, Kidney Transplantation; TAC, Tacrolimus; MMF, Mycophenolate; mTORi, mTOR inhibitors; CsA, Cyclosporine.

Table S3 – Hazard ratios for recipient, pancreas and kidney graft survival adjusted by dialysis lead time and diabetes lead time.

		95% CI		
Variable	HR	LL	UL	P
Recipient survival (adjusted by dialysis lead time)				
Dialysis before SPK (yes)	1.23	1.06	1.43	0.008
Preemptive	1.00			
< 12 months	1.01	0.84	1.21	0.93
≥ 12 months	1.32	1.15	1.53	< 0.0001
Recipient survival (adjusted by diabetes lead time)				
Dialysis before SPK (yes)	1.23	1.07	1.42	0.006
Preemptive	1.00			
< 12 months	1.11	0.92	1.33	0.28
≥ 12 months	1.28	1.09	1.49	0.002

DC, Death-censored; SPK, Simultaneous Pancreas-Kidney transplantation.

Table S4 – IPTW weighted hazard ratios for recipient survival, death-censored pancreas graft survival and death-censored kidney graft survival according for the periods 2000 – 2009 and 2010 – 2017.

		95% CI		
Variable	HR	LL	UL	P
Period 2000 - 2009				
Recipient survival				
Dialysis before SPK (yes)	1.75	1.24	2.49	0.002
Preemptive	1.00			
< 12 months	1.49	0.97	2.29	0.07
≥ 12 months	1.82	1.28	2.60	< 0.001
DC Pancreas graft survival				
Dialysis before SPK (yes)	0.98	0.74	1.29	0.89
Preemptive	1.00			
< 12 months	0.91	0.63	1.30	0.59
≥ 12 months	1.01	0.76	1.35	0.95
DC Kidney Graft Survival				
Dialysis before SPK (yes)	1.49	1.06	2.10	0.02
Preemptive	1.00			
< 12 months	1.26	0.82	1.93	0.30
≥ 12 months	1.58	1.12	2.24	0.01
Period 2010 - 2017				
Recipient survival				
Dialysis before SPK (yes)	1.75	1.24	2.49	0.002
Preemptive	1.00			
< 12 months	1.19	0.82	1.75	0.36
≥ 12 months	1.79	1.32	2.42	< 0.001
DC Pancreas graft survival				
Dialysis before SPK (yes)	1.16	0.95	1.42	0.15
Preemptive	1.00			
< 12 months	1.14	0.88	1.47	0.33
≥ 12 months	1.17	0.95	1.44	0.14
DC Kidney Graft Survival				
Dialysis before SPK (yes)	1.45	1.09	1.91	0.01
Preemptive	1.00			
< 12 months	1.22	0.86	1.74	0.26
≥ 12 months	1.51	1.14	2.01	0.004

DC, Death-censored; SPK, Simultaneous Pancreas-Kidney transplantation.

Table S5 - Recipient and donor baseline characteristics for preemptive KTA and preemptive SPK.

	Preemptive KTA (n = 3343)	Preemptive SPK (n = 1796)	*P*
Donor			
Age (years)	39.43 ± 12-37	25.46 ± 9.34	< 0.0001
Gender (male)	1494 (45)	1239 (69)	< 0.0001
Ethnicity			< 0.0001
Caucasian/Other	2405 (72)	1203 (67)	
African American	392 (12)	341 (19)	
Hispanic	466 (14)	216 (12)	
Asian	80 (2)	36 (2)	
BMI (kg/m^2)	27.14 ± 4.89	24.02 ± 3.98	< 0.0001
Smoking habit (yes)	776 (23)	198 (11)	< 0.0001
Hypertension (yes)	293 (9)	90 (5)	< 0.0001
Kidney CIT (h)	2 [1.00 – 11.25]	10.20 [7.75 – 13.92]	< 0.0001
KDPI	0.38 [0.19 – 0.62]	0.17 [0.07 – 0.31]	< 0.0001
Pancreas preservation time (h)	-	11.39 ± 5.63	-
PDRI	-	1.10 ± 0.38	-
SCr at donation (mg/dL)	1.13 ± 0.76	1.00 ± 0.69	< 0.0001
Serum Amylase (U/L)	-	66 [35 - 125]	-
Serum Lipase (U/L)	-	22 [13 - 59]	-
Serum AST (U/L)	-	46 [29 - 79]	-
Serum ALT (U/L)	-	34 [22 - 61]	-
Serum total bilirubin (mg/dL)	-	0.8 [0.5 – 1.2]	-
BUN (mg/dL)	-	14.01 ± 9.89	-
LDKT (yes)	2292 (69)	0 (0)	-
Cause of death			< 0.0001
Anoxia	263 (8)	323 (18)	
Cerebrovascular Event	300 (9)	287 (16)	
Head Trauma	457 (13)	1133 (63)	
Other	31 (1)	53 (3)	
Donor after cardiac death (yes)	122 (4)	53 (3)	0.57
Cardiac arrest after brain death (yes)	81 (8)	126 (7)	0.85
Recipient			
Age at transplantation (years)	46.22 ± 7.43	42.06 ± 7.70	< 0.0001
Gender (male)	2117 (63)	988 (55)	< 0.0001
Ethnicity			< 0.0001
Caucasian/Other	2169 (65)	1473 (82)	
African American	560 (17)	180 (10)	
Hispanic	490 (14)	107 (6)	
Asian	124 (4)	36 (2)	
BMI (kg/m^2)	29.33 ± 5.45	25.60 ± 3.81	< 0.0001
Diabetes Type			< 0.0001
Type 1	1365 (41)	1706 (95)	
Type 2	1978 (59)	63 (5)	
Diabetes duration at transplantation (years)	20.42 ± 11.29	28.87 ± 8.71	< 0.0001
Peripheral vascular disease (yes)	265 (8)	107 (6)	< 0.0001
Total HLA Mismatches	3.60 ± 1.75	4.52 ± 1.16	< 0.0001
Induction Immunosuppression			< 0.0001
Thymoglobulin	1421 (43)	1078 (60)	
Basiliximab/Daclizumab	675 (20)	198 (11)	
Alemtuzumab	489 (15)	251 (14)	
Other/No reported	758 (22)	269 (15)	

Data are mean ± SD, median [IQR] or n (%), unless otherwise specified. SPK, Simultaneous Pancreas-Kidney; KTA, Kidney Transplantation Alone; BMI, Body Mass Index; CIT, Cold Ischemia Time; KDPI, Kidney Donor Profile Index; PDRI, Pancreas Donor Risk Index; SCr, Serum Creatinine; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BUN, Blood Urea Nitrogen; LDKT, Living Donor Kidney Transplantation.

Table S6 – Standardized differences before and after IPTW adjustment for preemptive SPK and preemptive KTA recipients

	Before IPTW adjustment	After IPTW adjustment
Donor		
Age (years)	0.392	0.074
Gender (male)	0.403	- 0.065
BMI (kg/m^2)	0.113	0.027
Smoking habit (yes)	0.288	0.065
Hypertension (yes)	0.123	0.067
Kidney CIT (h)	- 0.493	- 0.095
LDKT (yes)	- 1.492	- 0.097
Recipient		
Age at transplantation (years)	0.001	0.001
Gender (male)	- 0.134	0.085
Ethnicity		
Caucasian/Other	- 0.290	- 0.097
African American	0.305	0.086
Hispanic	0.228	0.071
Asian	0.091	0.051
BMI (kg/m^2)	0.278	0.082
Diabetes Type	0.155	0.058
Diabetes duration at transplantation	-0.838	-0.082
Peripheral vascular disease (yes)	0.063	0.035
Total HLA Mismatches	0.001	0.001
Induction Immunosuppression		
Thymoglobulin	- 0.298	0.033
Basiliximab/Daclizumab	0.315	0.067
Alemtuzumab	0.033	- 0.017
Other/No reported	0.185	0.081

BMI, Body Mass Index; CIT, Cold Ischemia Time; KDPI, Kidney Donor Profile Index; LDKT, Living Donor Kidney Transplantation.

Table S7 – Unadjusted and IPTW weighted hazard ratios for recipient survival and death-censored kidney graft survival

		95% CI		
Variable	HR	LL	UL	*P*
Recipient survival				
Unadjusted				
Preemptive SPK	1.00			
Preemptive KTA	1.39	1.16	1.66	< 0.0001
IPTW adjusted				
Preemptive SPK	1.00			
Preemptive KTA	1.34	1.10	1.63	0.003
DC Kidney Graft Survival				
Unadjusted				
Preemptive SPK	1.00			
Preemptive KTA	0.94	0.77	1.15	0.56
IPTW adjusted				
Preemptive SPK	1.00			
Preemptive KTA	1.31	1.09	1.56	0.002

SPK, Simultaneous Pancreas-Kidney transplantation; KTA, Kidney Transplantation Alone; DC, Death-censored

Table S8 – Unadjusted and IPTW weighted hazard ratios for recipient survival and death-censored kidney graft survival according to donor type.

		95% CI		
Variable	HR	LL	UL	*P*
Recipient survival				
Unadjusted				
Preemptive SPK	1.00			
Preemptive LDKT	1.13	0.93	1.38	0.21
Preemptive DDKT	2.02	1.63	2.49	< 0.0001
IPTW adjusted				
Preemptive SPK	1.00			
Preemptive LDKT	1.25	1.002	1.58	0.048
Preemptive DDKT	1.43	1.15	1.77	0.001
DC Kidney Graft Survival				
Unadjusted				
Preemptive SPK	1.00			
Preemptive LDKT	0.88	0.72	1.09	0.24
Preemptive DDKT	1.08	0.84	1.38	0.57
IPTW adjusted				
Preemptive SPK	1.00			
Preemptive LDKT	0.73	0.57	0.93	0.01
Preemptive DDKT	1.74	1.44	2.10	< 0.0001

SPK, Simultaneous Pancreas-Kidney transplantation; KTA, Kidney Transplantation Alone; DC, Death-censored

Table S9 – Hazard ratios for recipient survival, death-censored pancreas graft survival and death-censored kidney graft survival for patients with T1D and T2D

		95% CI		
Variable	HR	LL	UL	P
Type 1 Diabetes				
Recipient survival				
Dialysis before SPK (yes)	1.38	1.19	1.32	< 0.0001
Preemptive	1.00			
DC Pancreas graft survival				
Dialysis before SPK (yes)	1.03	0.91	1.17	0.61
Preemptive	1.00			
DC Kidney Graft Survival				
Dialysis before SPK (yes)	1.49	1.26	1.76	< 0.001
Preemptive	1.00			
Type 2 Diabetes				
Recipient survival				
Dialysis before SPK (yes)	1.14	0.61	2.12	0.69
Preemptive	1.00			
DC Pancreas graft survival				
Dialysis before SPK (yes)	1.15	0.65	2.03	0.53
Preemptive	1.00			
DC Kidney Graft Survival				
Dialysis before SPK (yes)	1.47	0.71	3.03	0.30
Preemptive	1.00			

DC, Death-censored; SPK, Simultaneous Pancreas-Kidney transplantation.

Table S10– Hazard ratios for recipient survival for patients with T1D and T2D adjusted by diabetes lead time.

		95% CI		
Variable	HR	LL	UL	P
Type 1 Diabetes				
Recipient survival				
Dialysis before SPK (yes)	1.38	1.18	1.32	< 0.0001
Preemptive	1.00			
Type 2 Diabetes				
Recipient survival				
Dialysis before SPK (yes)	1.34	0.61	2.10	0.68
Preemptive	1.00			

T1D, Type 1 Diabetes; T2D, Type 2 Diabetes; SPK, Simultaneous Pancreas-Kidney transplantation.

Table S11 – IPTW adjusted logistic regression for any post-transplant complication and graft rejection for preemptive and non-preemptive SPK.

		95% CI		
	OR	LL	UL	*P*
Any post-transplant complication				
Dialysis before SPK (yes)	1.04	0.86	1.25	0.73
Local infection				
Dialysis before SPK (yes)	1.31	0.88	1.96	0.19
Anastomotic leak				
Dialysis before SPK (yes)	0.78	0.50	1.22	0.28
Pancreatitis				
Dialysis before SPK (yes)	0.74	0.51	1.06	0.10
Graft Vessel Thrombosis				
Dialysis before SPK (yes)	0.92	0.69	1.23	0.59
Bleeding				
Dialysis before SPK (yes)	0.49	0.25	1.00	0.05
Pancreas rejection				
Dialysis before SPK (yes)	1.23	0.99	1.53	0.07
Kidney rejection				
Dialysis before SPK (yes)	1.15	0.89	1.47	0.27

SPK, Simultaneous Pancreas-Kidney transplantation

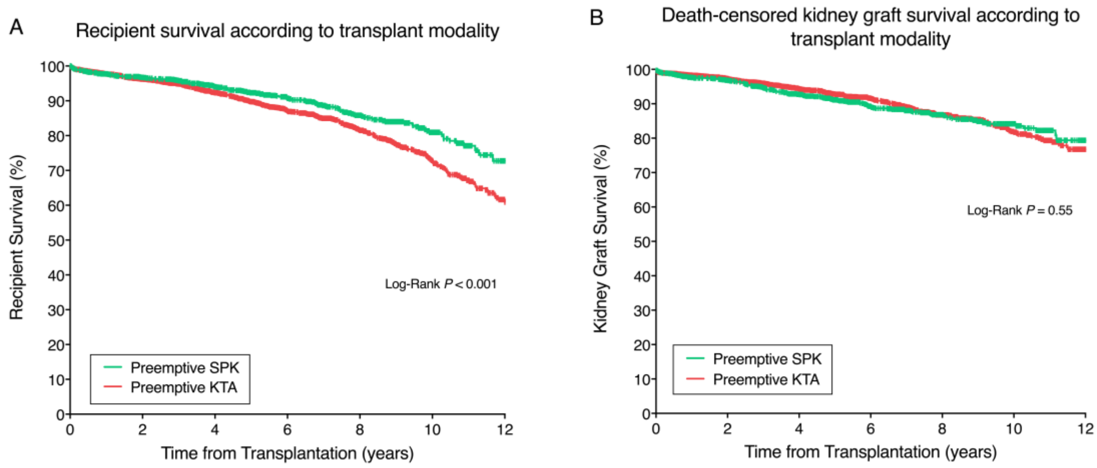


Figure S1. Recipient and kidney graft survival according to transplant modality and type of diabetes. A, Recipient survival according to transplant modality. B, Death censored kidney graft survival according to transplant modality. SPK, Simultaneous Pancreas-Kidney Transplantation; KTA, Kidney Transplantation Alone.

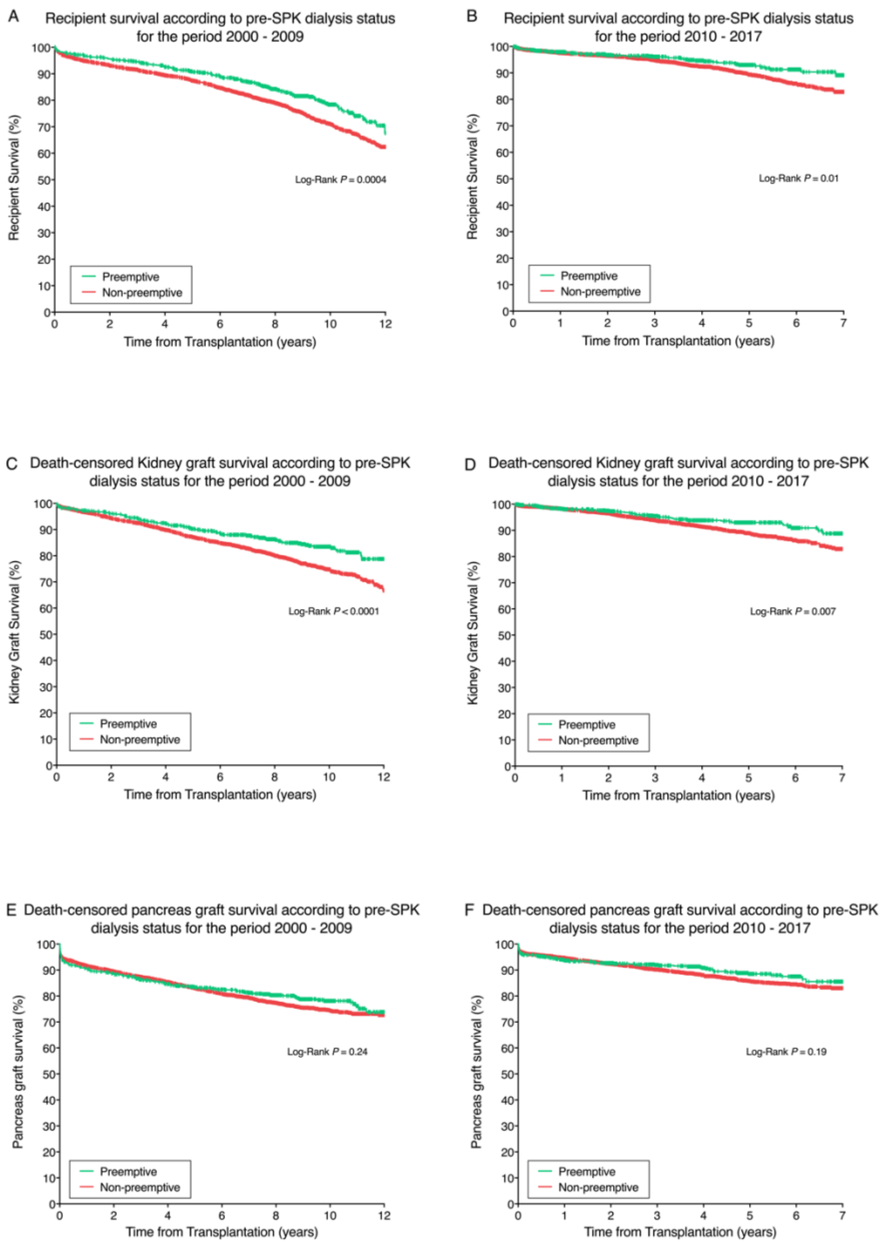


Figure S2. Recipient, pancreas and kidney graft survival according to pre-SPK dialysis status for two periods (2000-2009 and 2010-2017). A, Recipient survival according to pre-transplant dialysis status for the period 2000-2009. B, Recipient survival according to pre-transplant dialysis status for the period 2010-2017. C, Death-censored pancreas graft survival according to pre-transplant dialysis status for the period 2000-2009. D, Death-censored pancreas graft survival according to pre-transplant dialysis status for the period 2010-2017. E, Death-censored kidney graft survival according to pre-transplant dialysis status for the period 2000-2009. F, Death-censored kidney graft survival according to pre-transplant dialysis status for the period 2010-2017. SPK, Simultaneous Pancreas-Kidney Transplantation.

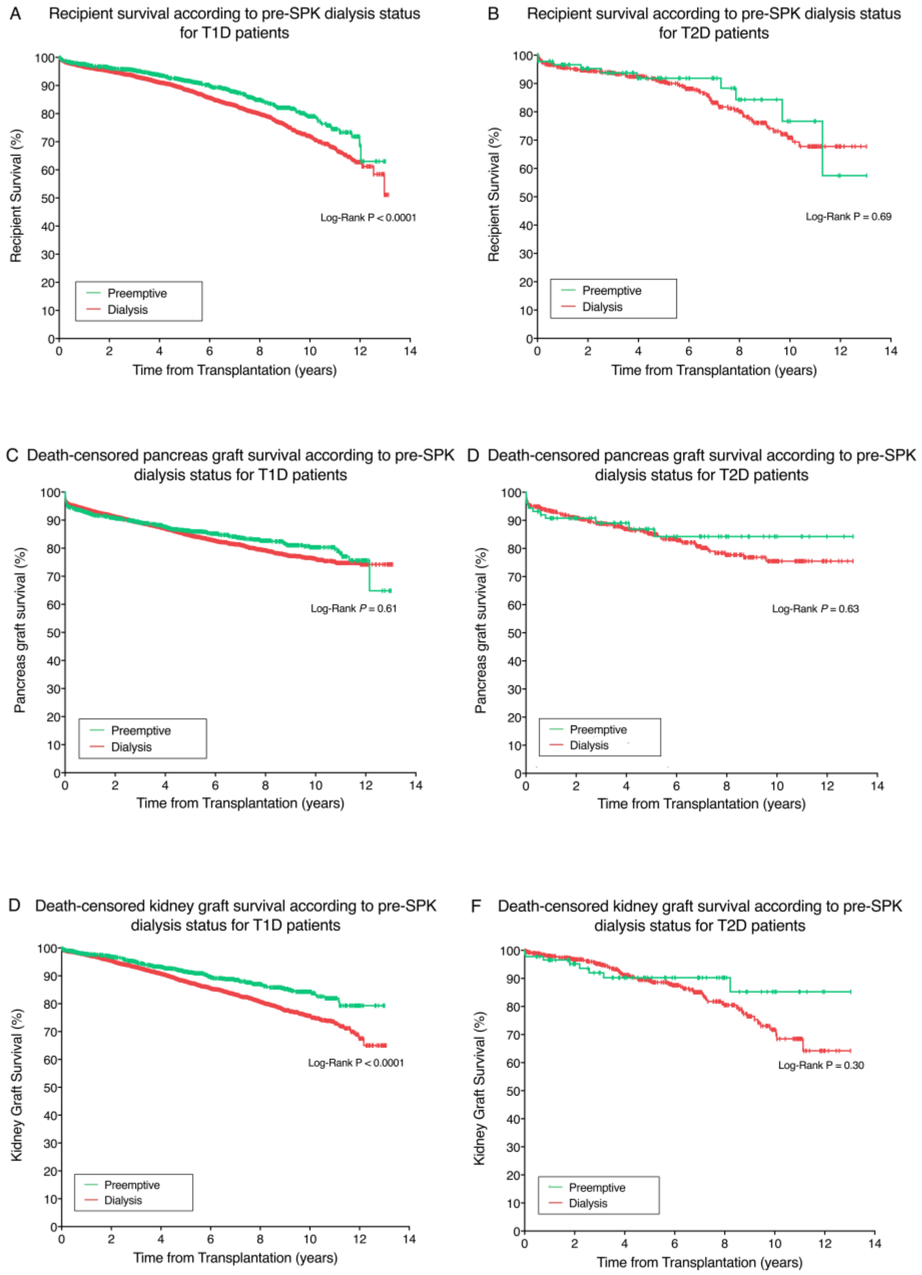


Figure S3. Recipient, pancreas and kidney graft survival according to pre-SPK dialysis status for T1D and T2D patients. A, Recipient survival according to pre-transplant dialysis status for T1D recipients. B, Recipient survival according to pre-transplant dialysis status for T2D recipients. C, Death-censored pancreas graft survival according to pre-transplant dialysis status for T1D recipients. D, Death-censored pancreas graft survival according to pre-transplant dialysis status for T2D recipients. E, Death-censored kidney graft survival according to pre-transplant dialysis status for T1D recipients. F, Death-censored kidney graft survival according to pre-transplant dialysis status for T2D recipients. SPK, Simultaneous Pancreas-Kidney Transplantation. T1D, Type 1 Diabetes; T2D, Type 2 Diabetes.