# Living Donor Kidney Transplantation Preceding Pancreas Transplantation Reduces Mortality in Type1 Diabetics with End-stage Renal Disease

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**Living Donor Kidney Transplantation Preceding Pancreas Transplantation Reduces Mortality in Type 1 Diabetics with End-stage Renal Disease**

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**Abbreviations:** (in alphabetical order)

ESRD: End-stage renal disease

LDKT: Living donor kidney transplantation

NGSP: National Glycohemoglobin Standardization Program

PAK: Pancreas after kidney transplantation

PTA: Pancreas transplantation alone

QOL: Quality of life

SPKT: Simultaneous pancreas-kidney transplantation

**Tables:** ___3___

**Figures:** ___4___ (color – No)

**Abstract**

**Background.** Simultaneous pancreas–kidney transplantation (SPK) is a definitive treatment for type 1 diabetics with end-stage renal disease (ESRD). Because of the shortage of deceased donors in Japan, the mortality rate during the waiting period is high. We evaluated mortality risk in patients with type 1 diabetes waiting for SPK, and the benefit of living donor kidney transplantation (LDK) preceding pancreas transplantation, which may reduce mortality in patients awaiting SPK.

**Materials and methods.** This retrospective study included 71 patients with type 1 diabetes. Twenty-six patients underwent SPK, 15 underwent LDK, and 30 were waiting for SPK. Their cumulative patient and graft survival rates were retrospectively evaluated. Risk factors contributing to mortality in patients with type 1 diabetes awaiting SPK were evaluated using a Cox proportional hazards model.

**Results.** The 5-year cumulative patient survival rates in the SPK and LDK groups were 100% and 93.3%, respectively ($P$=0.19), and 5-year kidney graft survival rates were 95.7% and 100% ($P$=0.46), respectively. The cumulative survival rate in patients awaiting SPK was 77.7% at 5 years of registration. Duration of dialysis was the only factor significantly associated with patient and graft survival by both univariate and multivariate analyses.

**Conclusion.** Patient and graft survival rates were similar in the SPK and LDK groups, but the survival rate of patients waiting SPK decreased over time. Duration of dialysis was an independent risk factor for patient and graft survival. LDK preceding pancreas transplantation may be an effective therapeutic option for patients with type 1 diabetes and ESRD.

## INTRODUCTION

Despite the increase in brain-dead organ donors in Japan after the amendment of the organ transplantation law in 2010, a severe shortage of donors remains a serious problem. This has resulted in long waiting periods and high mortality rates during waiting for transplantation [1].

According to the statistical data of the Japanese Pancreas and Islet Transplantation Association, the mean waiting period for pancreas transplantation in Japan is 1305 days. This compares unfavorably with the mean waiting period in Europe and the United States, which is <1 year. Of 194 patients are waiting for pancreas transplantation in Japan, 53 (27.3%) have already been waiting for >5 years.

Long-term dialysis in type 1 diabetes is inevitably accompanied by cardiovascular complications, which can be one of the factors to worsen the prognosis of type 1 diabetes. Held et al. have reported that patients with type 1 diabetes receiving dialysis have a life expectancy half that of a healthy person [2]. Longer duration of dialysis is generally associated with poorer patient prognosis [3], especially in type 1 diabetics with ESRD. Thus, early kidney transplantation from a living donor can be a leading option in Japan, where there are few brain-dead donors. Living donor kidney transplantation (LDK) preceding pancreas transplantation would be expected to enhance patient prognosis. We therefore evaluated the therapeutic utility of LDK preceding pancreas transplantation in patients awaiting simultaneous pancreas–kidney transplantation (SPK).

## MATERIALS AND METHODS

Seventy-six patients with type 1 diabetes were approved for pancreas transplantation at our institution by the Pancreas Transplantation Central Coordination Commission between April 1999 and March 2014. Five of these patients were excluded for cancellation of registration. Approval for SPK was based on clinical diagnosis, current and previous medical histories, family history, current medications, contraindications, evaluation of possible complications (including renal function, retinopathy, neural disturbance, arteriosclerotic lesions, and malignant disorders), and general medical condition. Approval also required pancreatic absolute endogenous insulin deficiency, as assessed by daily urinary C-peptide excretion or by a certain C-peptide level on glucagon stimulation tests.

Of the 71 included patients, 41 underwent transplantation, including 26 who underwent SPK and 15 who underwent LDK, including three who later underwent pancreas after kidney transplantation (PAK). The remaining 30 patients were still awaiting SPK.

The cumulative patient survival rates were retrospectively calculated for three groups: SPK, LDK, and those awaiting SPK. The cumulative kidney graft survival rates in the SPK and LDK groups were evaluated and compared. The cumulative survival of all 71 patients registered for SPK was evaluated and their long-term prognosis was evaluated by univariate and multivariate analyses.

JMP pro 11 (SAS Institute) was used for statistical analysis. Cumulative patient and graft survival rates were evaluated using the Kaplan–Meier method and compared using the log-rank test. The demographic and clinical characteristics of all 71 patients registered for SPK were evaluated, including age, sex, age at onset of type 1 diabetes, duration of type 1 diabetes (duration of insulin therapy), duration of dialysis, history of cardiovascular disease (CVD), history of infectious disease, glycosylated hemoglobin $A_{1c}$ ($HbA_{1c}$) (National Glycohemoglobin Standardization Program : NGSP), insulin concentration, LDK, and history of pancreas or kidney transplantation. Potential risk factors were evaluated by univariate and multivariate

analyses using a Cox proportional hazards model. $\chi^2$ tests were used to compare the demographic and clinical factors. Differences between two groups were determined using the Wilcoxon method. Statistical significance was defined as $P<0.05$.

## RESULTS

The demographic and clinical characteristics of the 71 patients registered for SPK are shown in Table 1. The cumulative survival rates of the SPK and LDK groups were 100 and 93.3%, respectively, at 1 year and 100 and 93.3%, respectively, at 5 years ($P=0.19$; Fig 1). One patient who underwent LDK died from a hypoglycemic coma during the follow-up. The 5-year death-censored kidney graft survival rates of the SPK and LDK groups were 95.7 and 100%, respectively ($P=0.46$; Fig 2). The cumulative survival rate in patients awaiting SPK was 77.7% at 5 years, decreasing rapidly thereafter to 66.1% at 6 years and 49.6% at 7 years (Fig 3). The cumulative survival rate in all 71 patients was 89.1% at 5 years (Fig 4). A total of 11 patients died during the waiting period, including six from sudden death, two from cerebrovascular disease, two from sepsis, and one from aspiration pneumonia after hypoglycemic coma.

Univariate and multivariate analyses using a Cox proportional hazards model were performed to identify factors associated with survival during the waiting period. Factors analyzed included patient age, sex, duration of diabetes (history of insulin therapy), $HbA_{1c}$ level, insulin level, duration of dialysis, history of CVD, history of infectious disease, and history of pancreas or kidney transplantation. Both univariate and multivariate analyses demonstrated that mean duration of dialysis was the only independent factor significantly predictive of survival during the waiting period (Tables 2 and 3).

## DISCUSSION

Initiation of dialysis drastically reduces patient survival rates. In Japan, the 5- and 10-year survival rates of patients undergoing dialysis are 59.4 and 36.3%, respectively, with low rates also observed in type 1 diabetes patients receiving

dialysis. We found that the 5-year survival rate of patients awaiting SPK was 77.7%, which was lower than that of the SPK and LDK groups, which was 100% and 93.3%, respectively. Patients initiating dialysis are at risk of developing complications such as CVD [4]. Pancreas and kidney transplantation decreases cardiovascular and neural complications [5,6] and improves patient prognosis. Although SPK, the primary therapeutic option, has been shown to benefit patients, it also has disadvantages, including its invasiveness, shortage of suitable donors, and resultant long-waiting period.

Kidney transplantation alone can moderately decrease cardiovascular complications caused by dialysis and improve quality of life (QOL). LDK is especially appropriate for patients with type 1 diabetes and severe complications, such as severe arteriosclerosis, which make SPK more difficult. In both LDK and SPK, their life-threatening risks become lower than that of dialysis, however, the operative risk of LDK becomes lower earlier than for SPK, at 15 and 101 days, respectively, after surgery [7]. LDK is less invasive than SPK and can be an effective treatment option. LDK has many other benefits: (1) there are some reports that patient and graft survival rates of LDK and SPK have little difference [8–10]; (2) LDK can reduce dialysis-associated complications and improve patient prognosis; (3) unlike a transplant from a brain-dead donor, LDK recipients can be preoperatively examined and undergo safe transplantation by elective operation; (4) the costs of transplantation are lower than those for dialysis in the 2nd and subsequent years [11]; and (5) physical and psychological QOL is drastically improved by transplantation [12,13]. In contrast, LDK has several drawbacks, first is the need for a living donor. However, this procedure has been shown to be safe for living donors, with no loss of renal function or life expectancy [14]. Second is the inability of recipients to stop insulin therapy, the instability of glycemic control, and the recurrence of type 1 diabetes [15,16]. In consideration of these advantages and disadvantages, cautious and appropriate decisions for surgery are required.

To date, 15 patients with type 1 diabetes have undergone LDK in our institution. Three of them had undergone successful PAK. There are advantages and disadvantages to PAK, thus careful assessment is required to judge the adaptation of surgery.

The advantages of PAK are that it is the best method to achieve insulin withdrawal [17]. It is particularly effective for brittle diabetes. Additionally, it has protective efficacy against diabetic complications, and prevents diabetic nephropathy of the kidney graft, arteriosclerosis, retinopathy, and autonomic neuropathy. It may also result in continuous improvement of prognosis. The disadvantages of PAK are that reoperation is necessary, and it may exacerbate kidney graft dysfunction because of operative invasion and immunosuppression. Generally, the following conditions are required when performing PAK: a physical state that can tolerate a second transplantation, no aggravation of cardiovascular complications [18], and well-maintained kidney graft function. In particular, good renal function is imperative, otherwise it may be lost even after successful pancreas transplantation. Kleinclauss et al. have proposed that renal function should be maintained, with a creatinine level <1.5 mg/dL with no proteinuria [19]. When concern about diabetic complications is resolved, although there is no clear limitation for the period of up to PAK, early subsequent pancreas transplantation after LDK is desirable, if possible within 1 year after LDK [20]. In addition, there are some reports that PAK is inferior to SPK in terms of patient and graft survival rates. However, the results of PAK are improved by immunosuppressants such as anti-thymocyte globulin [20–25].

In Japan, there is a shortage of brain-dead donors, therefore, LDK preceding pancreas transplantation should be able to prevent an extension of dialysis-related complications and decrease the mortality during the SPK waiting period. When performing PAK after LDK, because complications are inhibited by LDK, PAK can be performed under safe conditions.

## CONCLUSION

Patient and kidney graft survival rates were excellent in both SPK and LDK groups, with no significant differences. However, patient survival rate in those awaiting SPK decreased over time, especially after 5 years. Duration of dialysis was an independent mortality risk factor, indicating the need for early kidney transplantation. In line with this, LDK preceding pancreas transplantation may be an effective therapeutic option alternative to SPK for type 1 diabetics with ESRD when there

is a shortage of brain-dead donors, as in Japan.

**REFERENCES**

[1] Gruessner RWG, Sutherland DER, Gruessner AC. Mortality assessment for pancreas transplants. Am J Transplant 2004;4:2018–26.

[2] Held PJ, Akiba T, Stearns NS, Murumo F, Turrene MN, Maeda K, et al. Survival of middle-aged dialysis patients in Japan and the US, 1988-89. In: Friedman EA, editor. Developments in Nephrology, Volume 35, Death on Dialysis, Dordrecht: Kluwer Academic Publishers; 1994, p. 13–23.

[3] Navarro X, Sutherland DE, Kennedy WR. Long-term effects of pancreatic transplantation on diabetic neuropathy. Ann Neurol 1997;42:727–36.

[4] Raqqi P, Boulay A, Chertow GM, Amin N, Dillon M, Burke SK, et al. Cardiac calcification in adult hemodialysis patients: a link between end-stage renal disease and cardiovascular disease? 2002;39:695–701.

[5] Larsen JL, Colling CW, Ratanasuwan T, Burkman TW, Lynch TG, Erickson JM, et al. Pancreas transplantation improves vascular disease in patients with type 1 diabetes. Diabetes Care 2004;27:1706–11.

[6] Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 9;1998:S16–23.

[7] Ojo AO, Meier-Kriesche HU, Hanson JA, Leichtman A, Magee JC, Cibrik D, et al. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. Transplantation 2001;71:82–90.

[8] Reddy KS, Stablein D, Taranto S, Stratta RJ, Johnston TD, Waid TH, et al. Long-term survival following simultaneous kidney-pancreas transplantation versus kidney transplantation alone in patients with type 1 diabetes mellitus and renal failure. Am J Kidney Dis 2003;41:464–70.

[9] Young BY, Gill J, Huang E, Takemoto SK, Anastasi B, Shah T, et al. Living donor kidney versus simultaneous pancreas-kidney transplant in type 1 diabetics: an analysis of the OPTN/UNOS database. Clin J Am Soc Nephrol 2009;4:845–52.

[10] Kobayashi T, Gruessner AC, Wakai T, Sutherland DE. Three types of simultaneous pancreas and kidney transplantation. Transplant Proc 2014;46:948–53.

[11] Meier-Kriesche HU, Port FK, Ojo AO, Rudich SM, Hanson JA, Cibrik DM, et al. Effect of waiting time on renal transplant outcome. Kidney Int 2000;58:1311–7.

[12] Sureshkumar KK, Patel BM, Markatos A, Nghiem DD, Marcus RJ. Quality of life after organ transplantation in type 1 diabetics with end-stage renal disease. Clin Transplant 2006;20:19–25.

[13] Becker BN, Brazy PC, Becker YT, Odorico JS, Pintar TJ, Collins BH, et al. Simultaneous pancreas-kidney transplantation reduces excess mortality in type 1 diabetic patients with end-stage renal disease. Kidney Int 2000;57:2129–35.

[14] Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Guo H, et al. Long-term consequences of kidney donation. N Engl J Med 2009;360:459–69.

[15] Ishida-Oku M, Iwase M, Sugitani A, Masutani K, Kitada H, Tanaka M, et al. A case of recurrent type 1 diabetes with insulitis of transplanted pancreas in simultaneous pancreas-kidney transplantation from cardiac death donor. Diabetologia 2010;59:210–4.

[16] Vendrame F, Pileggi A, Laughlin E, Allende G, Martin-Pagola A, Damaris R, et al. Recurrence of type 1 diabetes after simultaneous pancreas-kidney transplantation despite immunosuppression is associated with autoantibodies and pathogenic autoreactive CD4 T-cells. Diabetes 2010;59:947–57.

[17] Kaufman DB. Pancreas-after-kidney transplantation: to have and not have not. Clin Transplant 2009;23:435–6.

[18] Chau K1, Martinez G, Elder GJ. Vascular calcification in patients undergoing kidney and simultaneous pancreas-kidney

transplantation.2014;19:275–81.

[19] Kleinclauss F, Fauda M, Sutherland DE, Kleinclauss C Gruessner RW, Matas AJ, et al. Pancreas after living donor kidney transplants in diabetic patients: impact on long-term kidney graft function. Clin Transplant 2009;23:437–46.

[20] Sampaio MS, Poommipanit N, Cho YW, Shah T, Bunnapradist S. Transplantation with pancreas after living donor kidney vs. living donor kidney alone in type 1 diabetes mellitus recipients. Clin Transplant 2010;24:812–20.

[21] Huang E, Wiseman A, Okumura S, Kuo HT, Bunnapradist S. Outcomes of preemptive kidney with or without subsequent pancreas transplant compared with preemptive simultaneous pancreas/kidney transplantation. Transplantation 2011;92:1115–22.

[22] Dinckan A, Aliosmanoglu I, Kocak H, Sari R, Erdogan O, Ertug Z, et al. Pancreas survival in simultaneous pancreas-kidney and pancreas-after-kidney transplantations: a five-year follow-up report. Ann Transplant 2012;17:14–9.

[23] Stratta RJ, Farney AC, Orlando G, Farooq U, Al-Shraideh Y, Rogers J. Similar results with solitary pancreas transplantation compared with simultaneous pancreas-kidney transplantation in the new millennium. 2014;46:1924–7.

[24] Larson TS, Bohorquez H, Rea DJ, Nyberg SL, Prieto M, Sterioff S, et al. Pancreas-after-kidney transplantation: an increasingly attractive alternative to simultaneous pancreas-kidney transplantation. 2004;77:838–43.

[25] Gruessner AC. 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). 2011;8:6–16.

**Table 1.** Demographic and clinical characteristics of the patient population

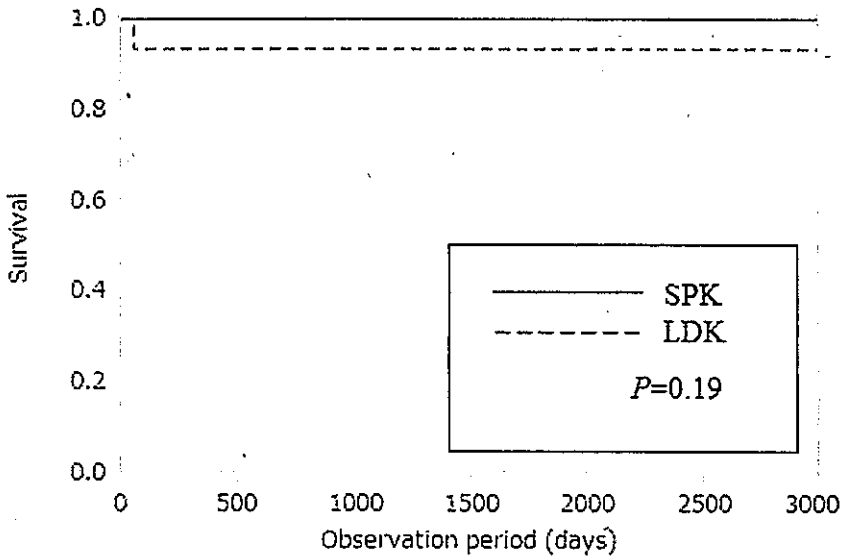
| Characteristics | SPK ($n$=26) | LDK ($n$=15) | Patients awaiting SPK ($n$=30) | $P$ value |
|---|---|---|---|---|
| Age, years | 36.4±7.4 | 41.5±8.3 | 42.3±8.3 | 0.013 |
| Sex (male:female) | 6:20 | 6:9 | 15:15 | 0.11 |
| Age at onset of type 1 diabetes, years | 15.7±8.2 | 14.6±6.5 | 14.6±7.2 | 0.86 |
| Duration of type 1 diabetes, years | 23.8±6.0 | 27.2±9.5 | 27.6±8.1 | 0.16 |
| Duration of dialysis, years | 5.6±4.0 | 2.8±3.0 | 12.4±8.4 | <0.001 |
| History of CVD | 2 (7.7%) | 2 (13.3%) | 7 (9.8%) | 0.85 |
| History of infectious disease | 2 (7.7%) | 0 (0%) | 5 (16.7%) | 0.10 |
| $HbA_{1c}$ (NGSP: %) | 7.5±1.5 | 7.6±1.6 | 7.9±1.6 | 0.63 |
| $HbA_{1c}$ (NGSP: ≥7.6%) | 50.0% | 33.3% | 60% | 0.23 |
| Insulin level, U | 30.5±10.0 | 34.2±13.8 | 28.6±9.1 | 0.25 |
| Observation period, days | 3685±1333 | 1373±1055 | 1837±1094 | <0.001 |

Results are mean±standard error of the mean

CVD = cardiovascular disease; $HbA_{1c}$ = glycosylated hemoglobin; LDK = living donor kidney transplantation; SPK = simultaneous pancreas–kidney transplantation

*$P$<0.05.

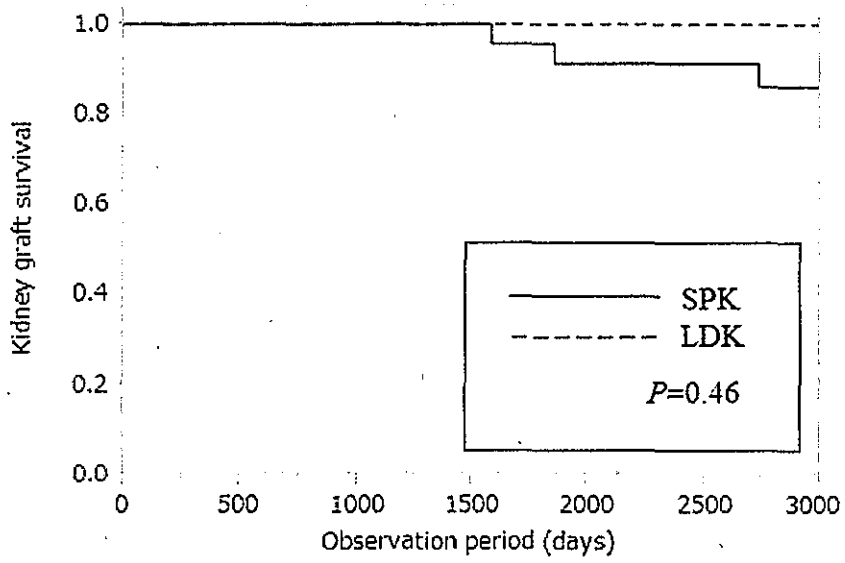
**Fig 1.** Kaplan–Meier analysis of cumulative survival rates in SPK and LDK groups.




Survival rates in SPK and LDK groups

| Category | N | 1-year | 5-year |
|---|---|---|---|
| SPK | 26 | 100% | 100% |
| LDK | 15 | 93.3% | 93.3% |

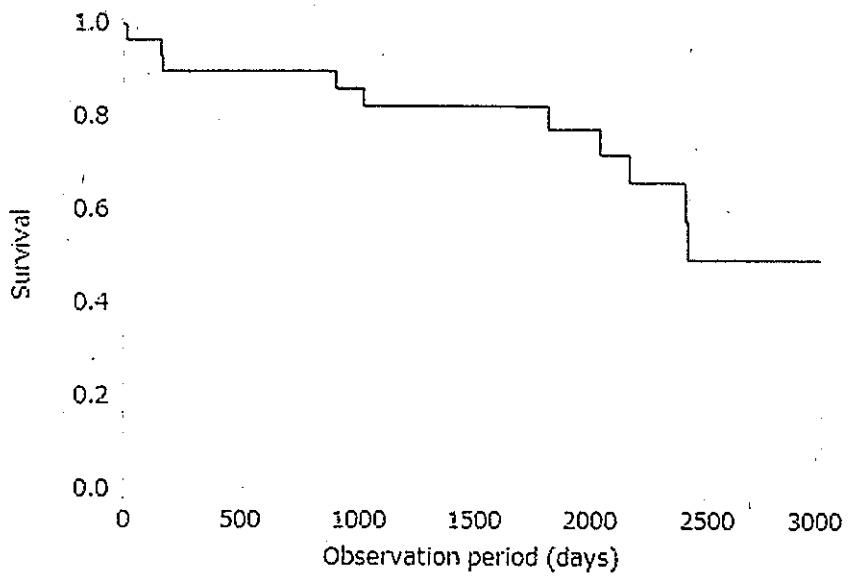
**Fig 2.** Kaplan–Meier analysis of death-censored kidney graft survival rates in SPK and LDK groups.




Kidney graft survival rates in SPK and LDK groups

| Category | N | 1-year | 5-year |
|---|---|---|---|
| SPK | 26 | 100% | 95.7% |
| LDK | 14 | 100% | 100% |

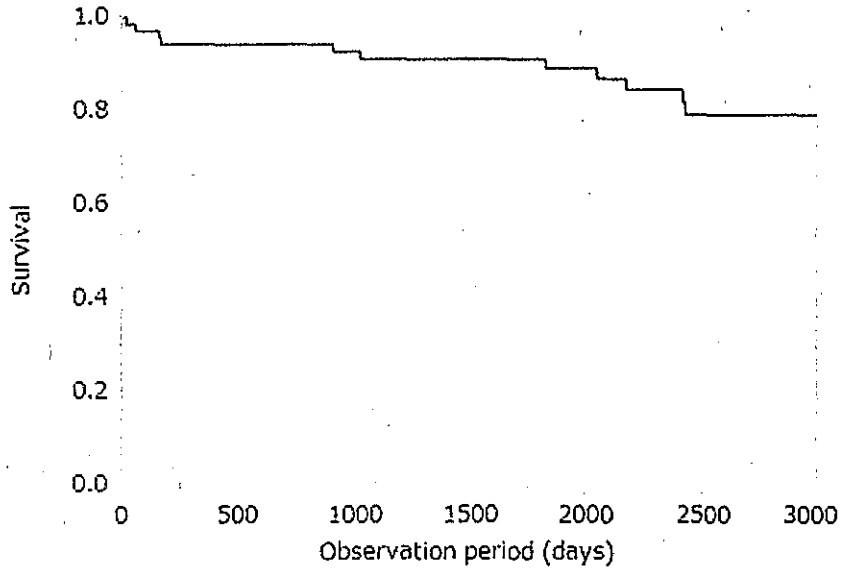
**Fig 3.** Kaplan–Meier analysis of cumulative survival rate in patients awaiting SPK.




Survival rate in patients awaiting SPK

| Category | N | 1-year | 5-year |
|---|---|---|---|
| Patients awaiting SPK | 30 | 90.0% | 77.7% |

**Fig 4.** Kaplan–Meier analysis of cumulative survival rate in all 71 patients registered for SPK.




Survival rate in all 71 patients registered for SPK

| Category | N | 1-year | 5-year |
|---|---|---|---|
| All patients registered for SPK | 71 | 94.4% | 89.1% |

**Table 2.** Univariate analysis of factors associated with mortality in patients with type 1 diabetes registered for SPK using a Cox proportional hazards model

| Variable | HR | 95% CI | *P* value |
|---|---|---|---|
| Age, years | 1.02 | 0.95–1.10 | 0.57 |
| Sex (male:female) | 0.98 | 0.26–3.11 | 0.97 |
| Age at onset of type 1 diabetes, years | 0.48 | 0.01–9.80 | 0.66 |
| Duration of type 1 diabetes, years | 1.00 | 0.93–1.08 | 0.90 |
| Duration of dialysis, years | 1.10 | 1.03–1.16 | 0.007 |
| History of CVD | 0.92 | 0.05–4.80 | 0.94 |
| History of infectious disease | 3.24 | 0.71–10.9 | 0.11 |
| $HbA_{1c}$ (NGSP: ≥7.6%) | 2.91 | 0.86–13.15 | 0.09 |
| Insulin level, units | 0.90 | 0.81–0.97 | 0.0059 |
| SPK | 1.66E-10 | 0.14–0.14 | <0.0001 |
| LDK | 0.60 | 0.032–3.17 | 0.60 |

*$P<0.05$

CI = confidence interval; CVD = cardiovascular disease; $HbA_{1c}$ = glycosylated hemoglobin; HR = hazard ratio; LDK = living donor kidney transplantation; SPK = simultaneous pancreas–kidney transplantation

**Table 3.** Multivariate analysis of factors associated with mortality in patients with type 1 diabetes registered for SPK using a Cox proportional hazards model

| Variable | HR | 95% CI | *P* value |
|---|---|---|---|
| Duration of dialysis, years | 1.09 | 1.01–1.17 | 0.0215 |
| History of CVD | 0.41 | 0.02–3.15 | 0.43 |
| History of infectious disease | 3.12 | 0.56–12.5 | 0.17 |
| $HbA_{1c}$ (NGSP: 7.6% and over) | 1.6 | 0.42–7.95 | 0.49 |
| LDK | 1.81 | 0.089–13.6 | 0.62 |

*$P<0.05$.

CI = confidence interval; CVD = cardiovascular disease; $HbA_{1c}$ = glycosylated hemoglobin; HR = hazard ratio; LDK = living donor kidney transplantation; SPK = simultaneous pancreas–kidney transplantation