ORIGINAL ARTICLE

Metabolic outcomes and renal function after simultaneous kidney/pancreas transplantation compared with kidney transplantation alone for type 2 diabetes mellitus patients

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SUMMARY

In this study, we aimed to compare the metabolic outcomes, renal function, and survival outcomes of simultaneous pancreas and kidney transplantation (SPK) and kidney transplantation alone (KTA) among end-stage kidney disease (ESKD) patients with type II diabetes mellitus (T2DM). Patients with ESKD and T2DM who underwent KTA ($n = 85$) or SPK ($n = 71$) in a transplant center were retrospectively reviewed. Metabolic profiles, renal function, and survival outcomes were assessed repeatedly at different follow-up time points. Propensity score procedures were applied to enhance between-group comparability. The levels of renal and metabolic outcomes between SPK and KTA over time were examined and analyzed using mixed-model repeated-measures approaches. The median follow-up period was 1.8 years. Compared with KTA, SPK resulted in superior metabolic outcomes and renal function, with lower levels of glycated hemoglobin (HbA1c; $P = 0.0055$), fasting blood glucose ($P < 0.001$), triglyceride ($P = 0.015$), cholesterol ($P = 0.0134$), low-density lipoprotein ($P = 0.0161$), and higher estimated glomerular filtration rate (eGFR; $P < 0.001$). SPK provided better metabolic outcomes and renal function. The survival outcomes of the recipients and grafts were comparable between the two groups.

Introduction

Type 2 diabetes accounts for the vast majority (approximately 90%) of diabetes worldwide [1] and is the primary cause of end-stage kidney disease (ESKD) [2]. In the United States, 90–95% of patients diagnosed with diabetes mellitus have type II diabetes (T2DM) [3].

Recently, the prevalence of diabetes in China has surged [4]. With the largest number of diabetic patients in the world, China ranked 1st on the list of adults with diabetes in the 2019 International Diabetes Federation Diabetes Atlas Report [1,4].

Since the first pancreas transplantation was performed at the University of Minnesota in 1966, and

with the improvements in surgical techniques and the introduction of immunosuppressive agents such as cyclosporine, the number of pancreas transplantations has increased steadily, especially for simultaneous pancreas and kidney transplantation [5–8]. For ESKD patients with T2DM, kidney transplantation alone (KTA) and simultaneous pancreas and kidney transplantation (SPK) are options [7]. In clinical scenarios, there is a lack of consensus on whether SPK or KTA should be recommended for T2DM patients with ESKD and what type of outcome they were expected to achieve; in particular, because of the obscure mechanism of T2DM, there is also a lack of consensus on whether the perioperative risks of the pancreas transplant procedure could be offset by the benefits of normal glycemic control. In the 2020 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline, SPK was recommended for candidates with ESKD and type 1 diabetes mellitus (T1DM), and few suggestions were available for ESKD patients with T2DM [9]. An Austrian study by Margreiter *et al.* [10] revealed that after adjusting for covariates of recipients and donors, no significant survival difference was observed between SPK and KTA among T2DM recipients. However, a recent study by Alhamad *et al.* [11] reported that after quantification by multivariable inverse probability of treatment weighted survival analyses, SPK recipients had better survival outcomes of kidney grafts and patients than KTA recipients. Han *et al.* [12] reported that the crude survival rates of SPK and KTA were significantly different. At present, little information is available regarding the comparison of the metabolic outcomes and renal function of SPK and KTA in T2DM patients, especially among the Chinese population who have the highest burden of T2DM. This study aimed to describe the characteristics of SPK and KTA recipients with T2DM in a single transplantation center in China and also to provide evidence for the comparison of the metabolic profiles, renal function, and survival outcomes between SPK and KTA.

Patients and methods

Study population and data collection

Transplantations for T2DM patients with ESKD from August 2015 to January 2020 at Tianjin First Central Hospital were retrospectively reviewed, with a total of 229 recipients identified. After excluding recipients below 18 years old and those who did not undergo primary transplantation, 156 participants with 71 SPK and 85 KTA were finally analyzed. The follow-up of this cohort ended in September 2020, and all participants were followed up for at least nine months. A flowchart of the selection process is presented in Fig. 1. All organs were obtained from deceased donors (DD), and no donors were prisoners at the time of organ procurement [13,14]. Organ donations were made after cardiac death (DCD) and brain and cardiac death (DBCD) and were commonly expressed as deceased donors (DD) in clinical practice and national databases in China [15,16]. Medical records were retrieved from the electronic medical documentation system of our center. To ensure consistent documentation, clinical records were collected by medical assistants and reviewed afterward by senior transplant doctors. Unclear cases are discussed in regular seminars. Follow-up information was obtained from the medical records or by phone contacts. The study was approved by the ethics committee of the hospital. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Baseline characteristics and comorbidities

Baseline clinical characteristics and comorbidities before transplantation were recorded at the time transplantation, including age, sex, body mass index (BMI) of the recipients and donors, recipients' type of dialysis, dialysis vintage, immunosuppressive induction and maintenance of drugs, the dose of insulin, fasting glucose level, C-peptide, panel-reactive antibodies (PRAs; positive/negative), and pretransplantation comorbidities. T2DM was based on the 1999 WHO guidelines and 2013 Guidelines for the prevention and control of type 2 diabetes in China [17,18]. The selection criteria for SPK candidates were based on the Chinese Pancreas Transplantation Guideline [19] which reported that if a T2DM patient with ESKD has the following: age <60 years, BMI <30 kg/m^2, effective insulin treatment, low risk of cardiovascular disease, and good adherence to treatment and diet, then they would be recommended to undergo SPK. The cardiac workups for candidates in our center are electrocardiogram, echocardiography, tests of troponin, lactic dehydrogenase, glutamic pyruvic transaminase (ALT), and glutamic oxaloacetic transaminase (AST). Dialysis vintage was defined as the period between the initiation of dialysis and transplantation. Regarding the PRA result, if the percentage of PRA was >10%, then the PRA result was positive, otherwise the PRA result was negative; pretransplantation comorbidities included cardiovascular diseases, cerebrovascular diseases, and hypertension.
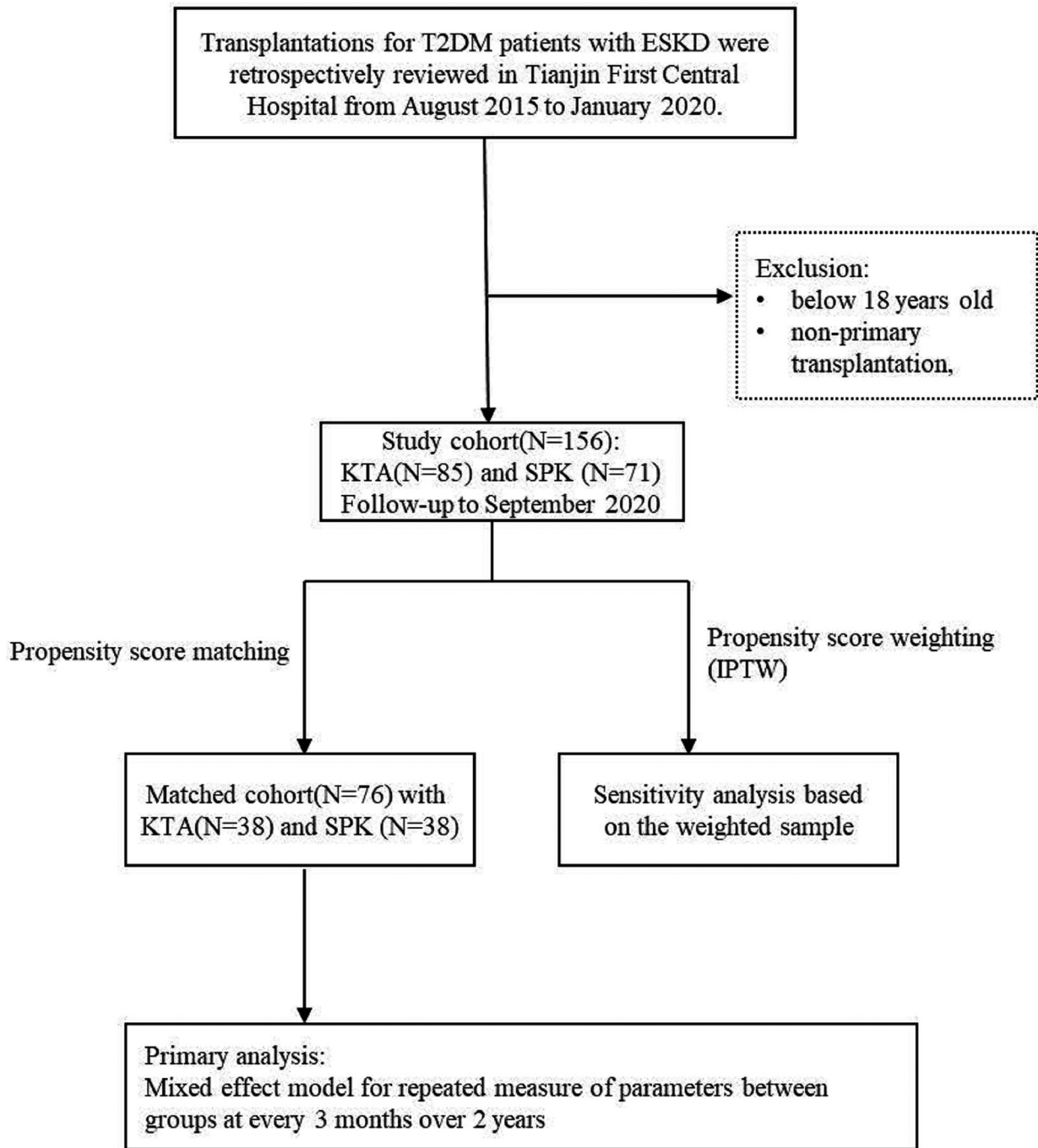
Figure 1 Flowchart of participant selection and analytic procedures.

Cardiovascular diseases were identified if there were previous myocardial infarctions and previous coronary interventions documented in the records. Patients with cerebrovascular diseases had documented transient ischemic attack (TIA) or ischemic stroke in their case histories. Hypertension was defined as blood pressure >140/90 mmHg or if a patient was treated with antihypertensive drugs.

Outcomes

The primary outcomes were metabolic outcomes, renal function, and survival outcomes after transplantation. Patients were followed up monthly for the first six months after transplantation and then once a year after 12 months. Renal graft failure was defined as patient death, kidney retransplantation, or return to dialysis.

Pancreatic graft failure was defined as resumption of the daily scheduled insulin, allograft pancreatectomy, or patient death. Renal function was evaluated by estimated glomerular filtration rate (eGFR) and was calculated based on the modification of diet in renal disease study equation (MDRD). Metabolic outcomes included glycated hemoglobin test percentage (HbA1c), fasting blood glucose level, triglyceride level, cholesterol level, and low-density lipoprotein (LDL) level. Complications included rejection, infection, cardiovascular diseases, cerebrovascular diseases, and surgical complications, including anastomosis, leak, bleeding, air embolism, and other surgery-related complications during the perioperative period. Rejection was diagnosed by biopsy. Delayed graft function (DGF) was diagnosed as returning to dialysis within seven days after transplantation.

Operation technique

Simultaneous pancreas and kidney was performed using a whole pancreas–duodenal and kidney graft procured from a multi-organ donor. The surgery was performed using the enteric drainage–systemic venous drainage technique under general anesthesia, and the grafts were placed intraperitoneally through a right rectus abdominal incision made on the same side. The gastroduodenal artery was reconstructed during donor dressing. The Y-graft of the donor iliac artery was used for artery reconstruction of the kidney and pancreas. The surgery method is provided in Fig. S1.

Immunosuppression

During the surgery, patients were induced with either anti-thymocyte globulin (rATG) plus steroids or interleukin 2 receptor monoclonal antibody (anti-IL-2R) with steroids. Based on the Chinese Pancreas Transplantation Guideline, for pretransplantation PRA(−) patients, anti-IL-2R was the prime choice, while for those with a high immunological risk, the rATG was preferred [19]. Following transplantation, the patients were treated with triple immunosuppressive regimens that included tacrolimus [Tac; or cyclosporine A (CsA) as an alternative], mycophenolate mofetil (MMF; or enteric-coated mycophenolate sodium or mizoribine as alternatives), and steroids. Empirically, rATG, Tac, and MMF were mostly administered to SPK recipients [20,21]. Regarding the steroid tapering protocol, steroid injection of 500 mg was administered consecutively during the first three days after transplantation. Subsequently, the recipients were administered an oral dose

of 20 mg. One month later, the oral dosage was reduced to 5–10 mg, depending on the individual's condition.

Statistical analysis

To minimize potential selection bias and enhance the comparability of study participants between KTA and SPK, a propensity score matching (PSM) procedure was implemented [22]. Propensity scores of the study subjects were estimated using a multivariable logistic regression model based on the baseline characteristics of the recipients and donors (Table 1). The nearest-neighbor 1:1 PSM with calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score was used. Furthermore, sensitivity analyses with a propensity score weighting procedure of the inverse probability of the treatment weighting (IPTW) (Table S1) were conducted. For IPTW, SPK recipients were weighted as the inverse of the estimated propensity, and KTA recipients were weighted as the inverse of one minus the estimated propensity score.

In view of the time-varying parameters (HbA1c, glucose level, triglyceride level, cholesterol, LDL, and eGFR) that were repeatedly assessed during the follow-up, a mixed-model analysis was performed, which used treatment groups, assessment time points, and the interaction of the treatment groups, with assessment time points as fixed effects and individual patients as a random effect [23].

All statistical analyses were performed using R Studio (Version 1.4.1106). Normally distributed continuous variables were expressed as the mean and standard deviation (SD) and compared using Student's t-test. Non-normally distributed data were presented as median and interquartile range (IQR) and compared using the Wilcoxon signed-rank test. Categorical variables were presented as absolute (n) and percentage (lrb%) values within each group and compared using the chi-squared test or Fisher's test. Kaplan–Meier analysis in the before-PSM cohort, after-PSM (matched) cohort, and in the IPTW-based sample (Table S2) was performed to assess and compare cumulative survival rates. Statistical significance was defined as a two-sided P-value <0.05.

Results

Patient characteristics before and after PSM

The baseline characteristics between the groups before and after PSM are reported in Table 1. Before PSM, a

Table 1. Baseline characteristics of the study patients before and after propensity score matching (PSM).

	Before PSM			After PSM		
	KTA (n = 85)	SPK (n = 71)	P	KTA (n = 38)	SPK (n = 38)	P
Recipients						
Recipient age [mean (SD)]	52.1 (8.3)	49.0 (8.0)	0.018	47.61 (11.38)	48.84 (7.84)	0.585
Recipient age-group						
≤50 year (%)	29 (34.1)	37 (52.1)	0.023	20 (52.6)	23 (60.5)	0.488
>50 year (%)	56 (65.9)	34 (47.9)		18 (47.4)	15 (39.5)	
Recipient gender = female (%)	14 (16.5)	7 (9.9)	0.228	8 (21.1)	4 (10.5)	0.208
Recipient BMI [mean (SD)]	25.0 (3.6)	24.5 (2.9)	0.425	25.45 (3.98)	24.63 (2.95)	0.313
Recipient BMI group (%)						
<18.5 kg/cm^2	3 (3.5)	1 (1.4)	0.185	2 (5.3)	0 (0.0)	0.139
[18.5–25 kg/cm^2]	42 (49.4)	41 (57.7)		16 (42.1)	22 (57.9)	
[25–30 kg/cm^2]	34 (40.0)	29 (40.8)		16 (42.1)	16 (42.1)	
[30–35 kg/cm^2]	5 (5.9)	0 (0.0)		3 (7.9)	0 (0.0)	
≥35 kg/cm^2	1 (1.2)	0 (0.0)		1 (2.6)	0 (0.0)	
Type of dialysis (%)						
Peritoneal dialysis	8 (9.4)	8 (11.3)	0.735	6 (15.8)	4 (10.5)	0.645
Hemodialysis	75 (88.2)	60 (84.5)		30 (78.9)	33 (86.8)	
None	2 (2.4)	3 (4.2)		2 (5.3)	1 (2.6)	
Dialysis vintage [month; median (IQR)]	12.0 [6.0, 24.0]	12.0 [5.0, 24.0]	0.399	12.00 [6.00, 24.00]	12.00 [5.00, 24.00]	0.481
Duration of T2DM [mean (SD)]	15.08 (8.18)	15.26 (5.26)	0.901	12.41 (7.23)	16.03 (5.67)	0.101
Dosage of insulin [U/day; mean (SD)]	17.00 (24.49)	25.51 (19.29)	0.069	13.28 (12.18)	23.63 (20.58)	0.058
Pre-op C-peptide [μmol/L; mean (SD)]	13.0 (6.0)	12.4 (7.6)	0.805	10.24 (5.40)	9.75 (6.14)	0.77
PRA(+) (%)	4 (4.7)	8 (11.3)	0.126	1 (2.6)	4 (10.5)	0.165
CVD before transplantation = yes (%)	26 (30.6)	22 (31.0)	0.957	9 (23.7)	11 (28.9)	0.602
CRD before transplantation = yes (%)	11 (12.9)	8 (11.3)	0.75	3 (7.9)	6 (15.8)	0.287
Hypertension before transplantation = yes (%)	6 (7.1)	12 (16.9)	0.148	36 (94.7)	37 (97.4)	0.556
Year of operation						
2015	6 (7.1)	3 (4.2)	0.009	3 (7.9)	3 (7.9)	0.49
2016	15 (17.6)	3 (4.2)		5 (13.2)	3 (7.9)	
2017	15 (17.6)	9 (12.7)		3 (7.9)	4 (10.5)	
2018	20 (23.5)	13 (18.3)		9 (23.7)	4 (10.5)	
2019	29 (34.1)	43 (60.6)		18 (47.4)	24 (63.2)	
Induction drugs						
rATG	8 (9.4)	68 (95.8)	<0.001	3 (7.9)	37 (97.4)	<0.001
Anti-IL-2R	77 (90.6)	3 (4.2)		35 (92.1)	1 (2.6)	
CNI (%)						
Tac	52 (61.2)	66 (93.0)	<0.001	26 (68.4)	36 (94.7)	0.003
CsA	33 (38.8)	5 (7.0)		12 (31.6)	2 (5.3)	
Antiproliferative drugs (%)						

Table 1. Continued.

	Before PSM			After PSM		
	KTA (n = 85)	SPK (n = 71)	P	KTA (n = 38)	SPK (n = 38)	P
MMF	25 (29.4)	34 (47.9)	0.021	13 (34.2)	20 (52.6)	0.135
EC-MPS	58 (68.2)	33 (46.5)		25 (65.8)	17 (44.7)	
Mizoribine	2 (2.4)	4 (5.6)		0 (0.0)	1 (2.6)	
Follow-up years	2.1 [1.5, 3.6]	1.5 [1.2, 2.2]	0.004	1.89 [1.32, 3.06]	1.71 [1.01, 2.71]	0.285
Donors						
Donor gender = female (%)	6 (7.1)	12 (16.9)	0.055	2 (5.3)	7 (18.4)	0.076
Donor age [years; mean (SD)]	47.1 (11.7)	32.1 (9.8)	<0.001	39.16 (10.08)	38.47 (7.24)	0.735
Donor age-group (%)						
<18 years	1 (1.2)	5 (7.1)	<0.001	1 (3.3)	4 (11.8)	0.345
[18–50 years]	49 (59.0)	64 (91.4)		29 (96.7)	29 (85.3)	
>50 years	33 (39.8)	1 (1.4)		0 (0.0)	1 (2.9)	
Donor BMI [kg/cm^2; mean (SD)]	23.1 (2.9)	22.3 (3.6)	0.177	23.52 (3.05)	22.61 (3.93)	0.306
Donor BMI group (%)						
<18.5 kg/cm^2	2 (2.8)	7 (10.8)	0.168	1 (3.3)	4 (11.8)	0.278
[18.5–30 kg/cm^2]	69 (95.8)	57 (87.7)		29 (96.7)	29 (85.3)	
≥30 kg/cm^2	1 (1.4)	1 (1.5)		0 (0.0)	1 (2.9)	
Kidney CIT [h; mean (SD)]	4.4 (1.5)	4.1 (1.2)	0.213	4.24 (1.38)	3.89 (0.92)	0.208

Anti-IL-2R, interleukin 2 receptor; CIT, cold ischemic time; CNI, calcineurin inhibitor; CsA, cyclosporine A; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; op, operation; PRA (+/−), if the percent panel-reactive antibody >10%, then the PRA is defined as positive, otherwise is negative; PSM, propensity score matching; SD, standard deviation; Tac, tacrolimus; WIT, warm ischemic time.
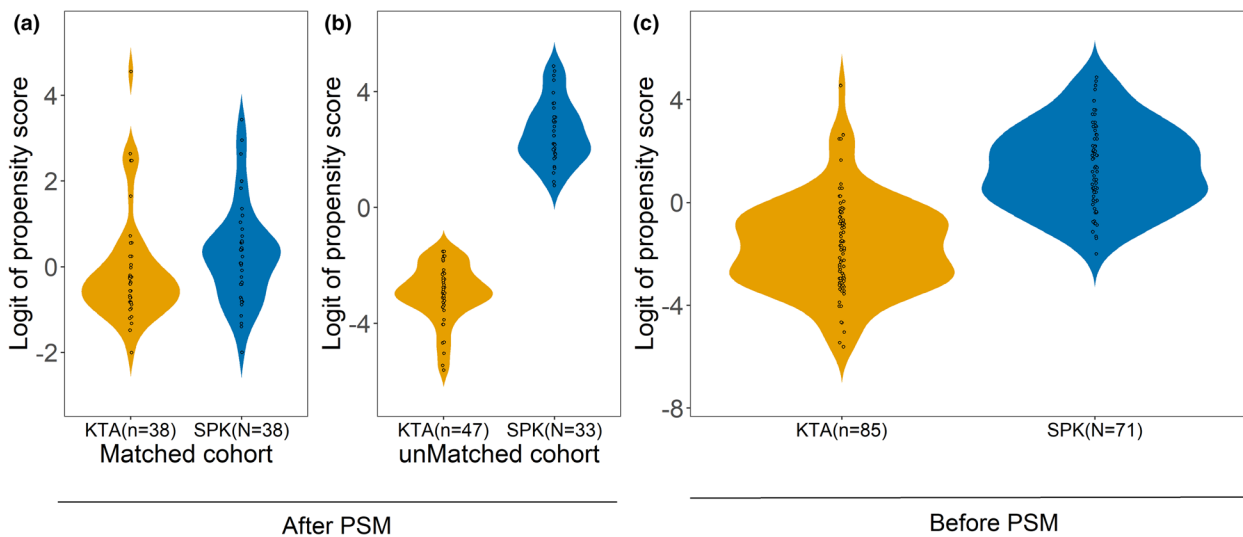
Figure 2 Plot of the distribution of the propensity score model in each group before and after propensity score matching (PSM).

total of 156 patients comprising 135 males and 21 females, with a mean age of 50.7 ± 8.3 years and BMI of 24.8 ± 3.3 kg/cm², were analyzed. Patients in both groups were diagnosed with ESKD secondary to diabetes. Compared with the KTA group, recipients and donors of the SPK group were younger, with mean age of 49.0 ± 8.0 years for SPK recipients vs. 52.1 ± 8.3 years for KTA recipients ($P = 0.018$) and 32.1 ± 9.8 years for SPK donors vs. 47.1 ± 11.7 years for KTA donors ($P < 0.001$). The majority of SPK cases were conducted in 2018 and 2019, which were significantly higher than those in the KTA group ($P = 0.009$). Factors such as recipient age, donor age, and years of surgery were used to calculate propensity scores in order to obtain a matched cohort. After PSM, 36 matched pairs of SPK and KTA were identified.

Figure 2. presents the distribution of the propensity score model for each group before and after PSM. The patients' baseline characteristics were comparable between the groups in the matched cohort (Table 1).

Immunosuppression strategy

Based on the matched sample, 97.4% of the SPK recipients were induced with rATG, while the majority of KTA recipients (92.1%) received anti-IL-2R ($P < 0.001$) during transplantation. Tac was administered to 94.7% of SPK recipients and to 68.4% of the KTA recipients ($P = 0.003$; Table 1). Of the SPK recipients, 52.6% were administered MMF and 44.7% were administered EC-MPS, while the majority of KTA recipients were administered EC-MPS (78.9%, $P = 0.135$; Table 1).

Table 2. Comparison of the renal function and metabolic parameters between KTA and SPK (based on the study sample after propensity score matching).

	KTA Baseline (SD)‡	SPK Baseline (SD)	KTA vs. SPK Mean difference over the levels of time (95% CI)†
HbA1c (%)	6.78 (2.18)	6.83 (1.52)	1.05 [0.7–104]**
Glucose level (mmol/l)	7.41 (4.51)	8.10 (4.24)	2.49 [1.81–3.17]***
Triglyceride (mmol/l)	2.42 (1.55)	2.28 (1.68)	0.65 [0.39–0.91]*
Cholesterol (mmol/l)	4.08 (1.28)	4.25 (1.08)	0.699 [0.42–0.98]*
LDL (mmol/l)	2.77 (1.22)	2.60 (0.93)	0.44 [0.26–0.62]*
eGFR (ml/min/l.73 m²)	6.42 (2.91)	7.08 (2.99)	−14.5 [−18.64 to −10.36]***

CI, confidence interval; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; SD, standard deviation.

*, **, and *** refer to *P*-value <0.05, <0.01, and <0.001, respectively.

†For assessing repeated clinical outcome changes at every 3 months over the 1-year follow-up, mixed-model analysis was carried out.

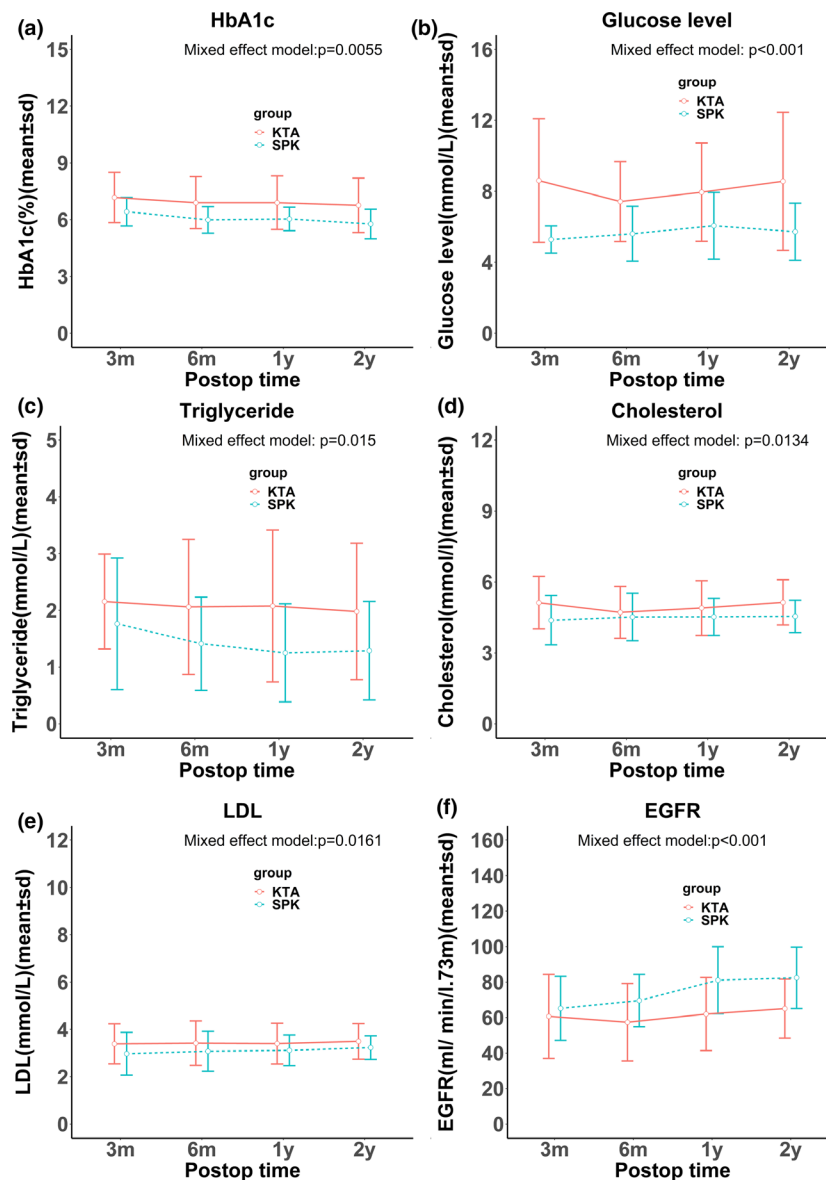‡For comparing the baseline values, two-sample *t*-test was used.

Figure 3 Comparison of HbA1c, blood glucose, LDL, triglyceride, cholesterol, and eGFR between the SPK and the KTA groups in the matched cohort.

Renal graft function and metabolic outcomes

The median follow-up years were 1.89 (1.32, 3.06) vs. 1.71 (1.01 and 2.71, respectively) ($P = 0.285$) for KTA and SPK, respectively, in the matched cohort (Table 1). The baseline levels of HbA1c, glucose, triglyceride, cholesterol, LDL, and the eGFR between the two groups were equivalent to each other (Table 2). After transplantation, the levels of metabolic outcomes over the follow-up period were significantly higher in the KTA group (Table 2; Fig. 3a–f). The average difference of HbA1c, glucose level, triglyceride, cholesterol, and LDL during the two years after transplantation were 1.05% [95% CI: (0.7–104)], 2.49 [95% CI: (1.81–3.17)] mmol/l, 0.65 [95% CI: (0.39–0.91)] mmol/l, 0.699 [95% CI: (0.42–0.98)] mmol/l, and 0.44 [95% CI: (0.26–0.62)] mmol/l, respectively. In terms of eGFR, both KTA and SPK showed an apparent rising trend after transplantation, with a significant increase of 14.5 [95% CI: (18.64–10.36)] ml/min/l.73 m^2 in the SPK group (Table 2; Fig. 3a–f). The sensitivity analysis of the IPTW weighting procedure showed consistent results (Table S1). Generally, there was an obvious benefit of SPK compared to KTA in terms of renal function.

Table 3. Survival comparison of the recipients and grafts between the SPK group and the KTA group before PSM.

	Before PSM			After PSM		
	KTA (*n* = 85)	SPK (*n* = 71)	*P*	KTA (*n* = 38)	SPK (*n* = 38)	*P*
Patient						
1-year	97.60%	98.60%	0.68	97.40%	100.00%	0.32
3-year	97.60%	98.60%		97.40%	100.00%	
Number of patient death	2	1		1	1	
Cause of patient death:	Respiratory failure because of pulmonary infection at 1st month after KTA; myocardial infarction at the 6th month after KTA	Myocardial infarction at 1st week after SPK		Myocardial infarction at the 6th month after KTA	Myocardial infarction at 1 week after SPK	
Kidney graft						
1-year	97.60%	95.50%	0.5	97.40%	100.00%	0.32
3-year	97.60%	95.50%		97.40%	100.00%	
Number of kidney graft loss	2	3		1	0	
Causes of kidney graft loss	Patient death	Patient death; thrombosis of graft's artery at the 1st month after SPK; chronic graft dysfunction at the 8th month after SPK				
Pancreas graft						
1-year		95.80%			97.40%	
3-year		95.80%			97.40%	
Number of pancreas graft loss	–	3			1	
Causes of pancreas graft loss	–	Patient death; thrombosis of pancreas graft at 2nd day after SPK; chronic graft dysfunction at the 10th month after SPK			Patient death	

Survival outcomes

In the original before-PSM cohort, one SPK recipient died because of myocardial infarction in the 1st week after the surgery, and two KTA recipients died because of myocardial infarction at the 6th month and respiratory failure following pulmonary infection at the 1st month after the surgery, respectively (Table 3; Fig. 4). In the SPK group, three renal graft losses were caused by patient death, thrombosis at the 1st month, and chronic graft dysfunction at the 8th month, with a three-year renal graft survival rate of 95.5% (Table 3; Fig. 4). Pancreatic graft loss was because of patient death, thrombosis of the pancreas graft on the 2nd day after surgery, and chronic graft dysfunction at the 10th month. The three-year renal graft survival rate was 95.8% (Table 3; Fig. 4). In the matched cohort and IPTW sensitivity analysis, the between-group survival rates were comparable (Table 3; Fig. 5; Table S2).

Complications

Regarding post-transplantation complications in the matched cohort, the rate of infection was significantly higher in the SPK group (44.7% vs. 15.8%, *P* = 0.006; Table 4). The rates of DGF, rejection, surgical complications, cardiovascular diseases after transplantation, cerebrovascular diseases after transplantation, and hypertension after transplantation were not significantly different (Table 4).
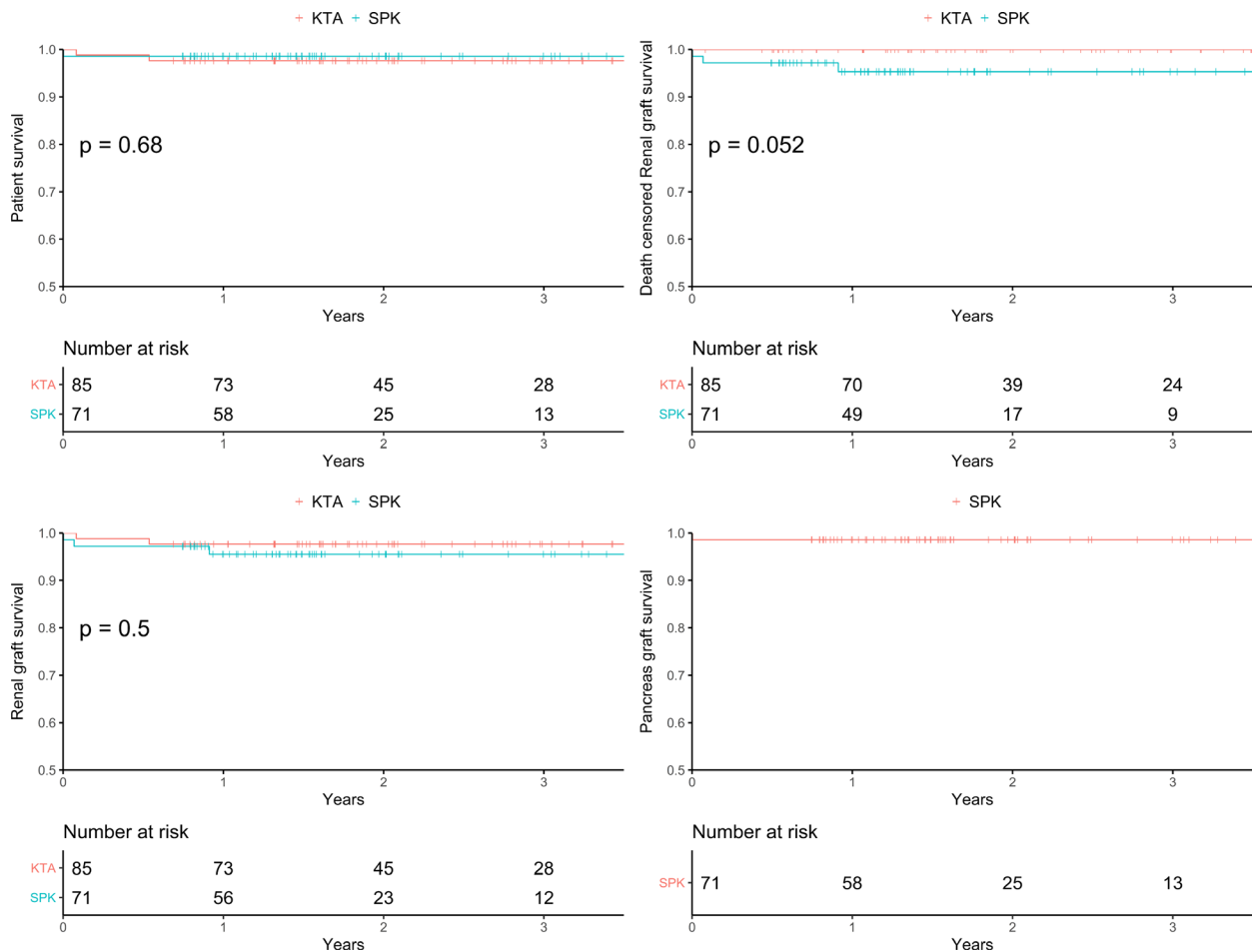
Figure 4 Comparison of recipients' and renal grafts' survival rates between the SPK and KTA groups in the after-PSM cohort.

Discussion

This study analyzed the characteristics and outcomes of patients with T2DM undergoing SPK or KTA between 2015 and 2020 in a transplantation center in China. The PSM procedure was adopted to minimize the imbalance between the two groups, and after PSM, the distribution of baseline characteristics was homogenous between the two groups. Renal function was significantly superior in the SPK group with a median follow-up period of approximately 2 years. Regarding the metabolic profiles, the levels of HbA1c, blood glucose, LDL, triglyceride, and cholesterol were significantly higher in the KTA group. Regarding survival outcomes, the three-year patient and graft survival rates were comparable between the two groups.

The selection criteria for SPK candidates with T2DM in this cohort were based on the Chinese Pancreas Transplantation Guideline [19], which were primarily based on the onset age of T2DM, BMI, risk of cardiovascular diseases, and insulin demand, and were consistent with those of other transplant centers, which generally focused on fasting C-peptide levels, BMI, age, insulin demand, and the absence of serious cardiovascular diseases [24–26]. However, besides age, BMI, and cardiovascular disease prevalence before transplantation that were similar between the two groups in our cohort, those from previous studies were quite divergent, in which the KTA recipients were generally in worse conditions with older age, higher BMI, higher rate of cardiovascular diseases before transplantation, longer waiting time, or longer dialysis vintage than the SPK group [10–12,27,28]. This was probably because of the prevalence of low BMI among T2DM patients in China [4]. A 2017 nationwide epidemiological survey reported that Chinese diabetic patients have a mean BMI of 24.9 ± 5.2 kg/cm^2, notably lower than that in European populations [4,29]. From this perspective, SPK would be promising for treating T2DM patients with ESKD in the Chinese population.
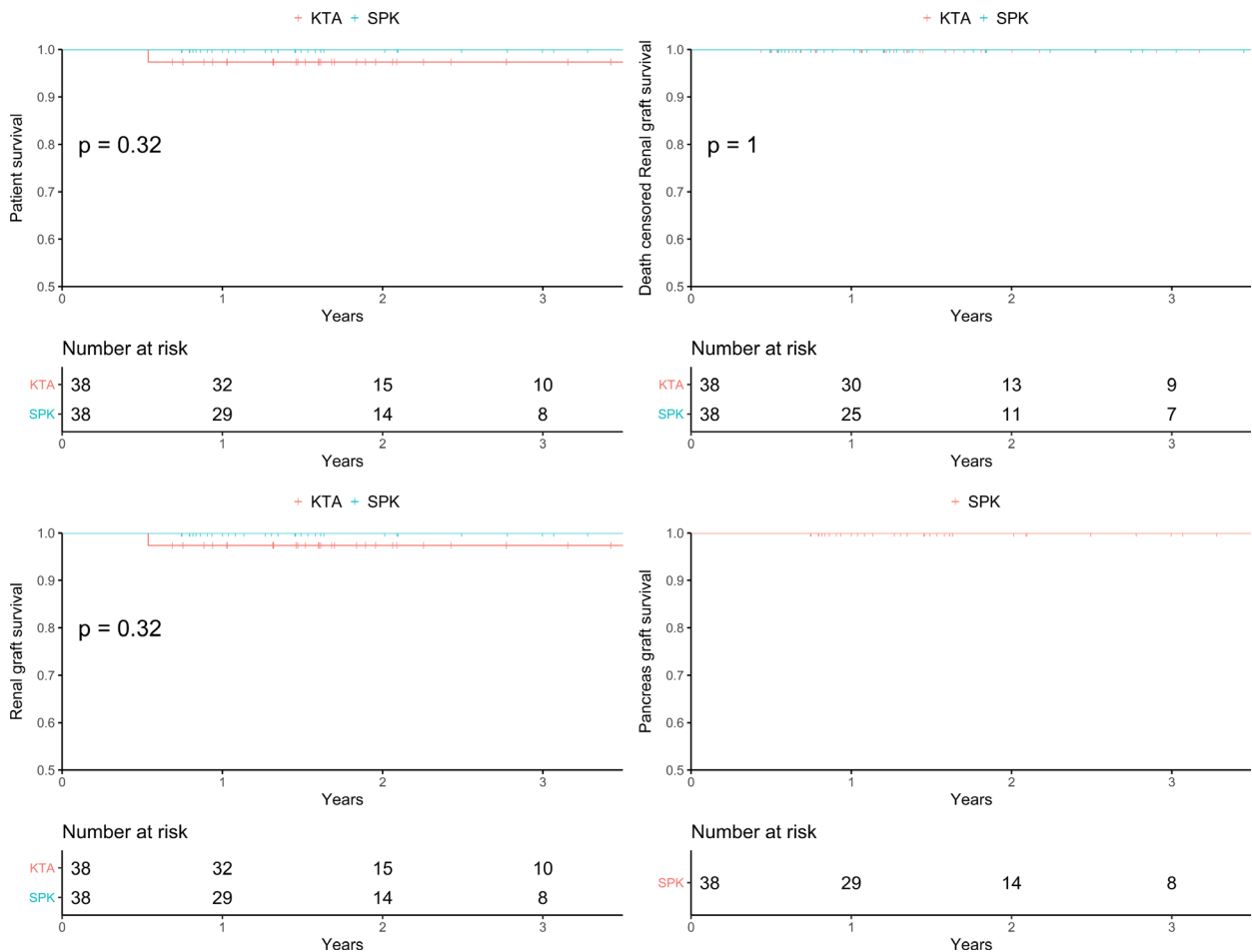
Figure 5 Comparison of recipients' and renal grafts' survival rates between the SPK and KTA groups in the before-PSM cohort.

Table 4. Comparison of the complications between the SPK and the KTA group before and after PSM.

	Before PSM			After PSM		
	KTA (*n* = 85)	SPK (*n* = 71)	*P*	KTA (*n* = 38)	SPK (*n* = 38)	*P*
Surgical complications = yes (%)	1 (1.2)	3 (4.2)	0.23	0 (0.0)	1 (2.6)	0.314
Rejection = yes (%)	8 (9.4)	6 (8.5)	0.834	4 (10.5)	4 (10.5)	>0.05
Infection = yes (%)	19 (22.4)	27 (38.0)	0.033	6 (15.8)	17 (44.7)	0.006
Abdominal infection	1 (1.2)	4 (5.6)		0 (0.0)	3 (7.9)	
Respiratory infection	8 (9.4)	9 (12.7)		4 (10.5)	6 (15.8)	
Urinary infection	7 (8.2)	7 (9.9)		2 (5.3)	4 (10.5)	
Other types of infection	3 (3.5)	7 (9.9)		0 (0.0)	4 (10.5)	
CVD after transplantation = yes (%)	25 (29.4)	21 (29.6)	0.982	10 (26.3)	10 (26.3)	>0.05
CRD after transplantation = yes (%)	11 (12.9)	9 (12.7)	0.961	4 (10.5)	7 (18.4)	0.328
DGF = yes (%)	3 (3.5)	1 (1.4)	0.404	1 (2.6)	1 (2.6)	>0.05
Hypertension after transplantation = yes (%)	83 (97.6)	68 (95.8)	0.508	37 (97.4)	35 (92.1)	0.304

CRD, cerebrovascular diseases; CVD, cardiovascular diseases; DGF, delayed graft function (for kidney graft).

Few studies have specifically compared the metabolic outcomes and renal function between KTA and SPK among T2DM patients. Hau *et al.* [12] examined the short- and long-term effects on metabolic control and beta cell function in T1DM and T2DM patients after SPK and T2DM patients with KTA. However, a detailed

comparison of the metabolic outcomes between the SPK and KTA groups has not been reported. The renal function comparison between SPK and KTA showed that creatinine level was higher in the KTA group during the first three months and remained insignificant in the following years [12]. In our study, the metabolic profiles of HbA1c, LDL, triglyceride, and cholesterol were consistently significantly higher in the KTA group after transplantation, with baseline levels being identical. This might be explained by the fact that compared with the KTA group, the SPK recipients had better islet function, which effectively improved blood glucose and lipid metabolism, relieved symptoms of hypertension, and reduced the occurrence of cardiovascular diseases and hyperlipidemia [30]. There were no significant differences in results of metabolism-related complications such as cardiovascular disease, cerebral diseases, and hypertension after transplantation between both groups. Longer-term follow-up of this cohort will be important because the incidence of hyperglycemia-related complications might increase over time with T2DM.

Regarding the post-transplant complications, the infection rate in the SPK group was higher than that in the KTA group in this study. This could be explained by the recommended induction agent of ATG for SPK [20,21,31]. The rate of DGF was significantly higher in the KTA group. In previous studies, DGF was proven to occur more frequently in KTA recipients, and DGF of the kidney was an independent risk factor for patient survival and kidney graft survival [10,12,28,32].

The survival outcomes of patients and grafts were comparable between the two groups. For kidney graft loss, there were numerically more patient death-censored renal graft losses in the SPK group, even though the study was not powered for these comparisons. Margreiter *et al.* and Hau *et al.* [12,33] reported that the raw survival outcome of SPK was significantly higher than that of KTA, with three-year survival rates of approximately 80% in the SPK group and 70% in the KTA group. After multivariable adjustment, Margreiter *et al.* showed that there were no significant differences in survival outcomes. Alhamad *et al.* [11] reported that after adjusting for multiple factors with multivariable inverse probability of treatment weighted survival analyses, the survival outcome of SPK was significantly higher. Except what was adjusted in the study by Alhamad *et al.*, other covariates such as duration of DM, insulin amount before transplantation, donor sex, donors' cause of death, waiting time, and metabolic variables such as cholesterol, triglyceride, and pre-

transplantation comorbidities should also be adjusted in future studies.

This study is the first attempt to compare metabolic outcomes and renal function after SPK or KTA in T2DM patients in China, which has the largest DM burden worldwide. Another advantage was that the study collected granular data on metabolic outcomes, which presented a comparison of the metabolic profiles of T2DM transplant recipients. However, this study has several limitations. The major limitation was the short follow-up period, which was not enough to observe the occurrence of the hard endpoints of treatments (e.g., chronic complications, patient death, and graft failure), as they usually take longer to be adequately monitored. Long-term follow-up is therefore warranted and is ongoing. Another limitation was the retrospective design of the study. Rigorous propensity score procedures (matching and weighting) were implemented to minimize confounding and bias and to enhance between-group comparability. However, some factors may still be missing or sub-optimally measured (i.e., patients' economic status, which might impact their attitudes toward SPK). A prospective study design with a randomized study design would strengthen this interpretation. Second, the sample size of the study was small, especially after PS, which limits the generalizability of the results. Future multicenter studies are necessary. However, considering that SPK is a rare procedure with a median annual center volume of less than 10 transplants [34], evidence-based guidelines and protocols were not sufficient, and there might be a large between-center variation; therefore, an applicable multicenter design would be tricky.

Conclusion

For T2DM patients with ESKD, SPK can improve renal and metabolic outcomes compared with KTA, with a median follow-up of approximately 2 years. SPK also provides comparable survival outcomes for both recipients and renal grafts with the KTA group. Additionally, in clinical practice, for T2DM patients combined with ESKD, considering the postoperative metabolic function and renal function, SPK would be a superior choice.

Authorship

YXF: obtained the funding, designed the study, interpreted the data, and wrote the manuscript. YC: conducted the data analysis and assisted with the data

interpretation manuscript writing. HW, JZ, ZW, CBM, XFS, GF and WLS: assisted with the data collection, data interpretation, and manuscript editing. YXF: was the guarantor of this work and, as such, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Sensitivity analysis 1: IPTW-based sample.
Table S2. Sensitivity analysis 2: IPTW survival outcomes.
Figure S1. Surgical technique.

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