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Kidney Delayed Graft Function in Simultaneous Pancreas-Kidney Transplant Recipients Is Associated With Inferior Outcomes

Sofia Nehring Firmino, MS,[1,2] Ekaterina Fedorova, MD,[2] Eman A. Alshaikh, MBBS,[3] Dixon Kaufman, MD, PhD,[2] Jon Odorico, MD,[2] Didier Mandelbrot, MD,[3] Brad C. Astor, PhD,[3,4] and Sandesh Parajuli, MD[3]

Background. Kidney delayed graft function (K-DGF) is associated with worse outcomes in simultaneous pancreas-kidney (SPK) recipients. However, its potential association with specific infections, rejection, and early complications remains unclear. **Methods.** We compared recipients with K-DGF to those without K-DGF among all adult SPK recipients transplanted at our center between January 2000 and December 2022 who had >2 wk of pancreas graft survival. Outcomes of interest included common posttransplant infections, including urinary tract infection (UTI), pneumonia, cytomegalovirus, BK, surgical wound infection, infected intra-abdominal fluid collection, graft rejection, and death-censored graft failure (DCGF) within the first year of transplant. We also looked for the need for early laparotomy within 90 d. **Results.** Seven hundred sixty-five SPK recipients were included, of whom 85 (11.1%) developed K-DGF. In Cox regression analysis, after adjustment for multiple key variables, K-DGF was associated/related with increased risk for UTI (adjusted hazard ratio [aHR], 1.76; 95% confidence interval [CI], 1.06-0.94; $P = 0.03$), infected intra-abdominal fluid collection (aHR, 2.14; 95% CI, 1.13-4.04; $P = 0.02$), and need for relaparotomy within 90 d (aHR, 2.07; 95% CI, 1.27-3.37; $P = 0.003$). K-DGF was also associated with increased risk for pancreas DCGF (aHR, 4.88; 95% CI, 1.90-12.51; $P < 0.001$). K-DGF was not associated with risk for other common infections of interest or graft rejection. **Conclusions.** K-DGF among SPK recipients is associated with an increased risk of UTI, infected intra-abdominal fluid collection, and the need for early relaparotomy, along with pancreas DCGF. Close monitoring and appropriate management are warranted in this higher-risk patient population.

(*Transplantation Direct* 2025;11: e1797; doi: 10.1097/TXD.0000000000001797.)

Received 28 October 2024. Revision received 6 March 2025.

Accepted 7 March 2025.

[1] University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI.

[2] Division of Transplant Surgery, Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI.

[3] Division of Nephrology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI.

[4] Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI.

This study was supported by an unrestricted research grant from the Virginia Lee Cook Foundation (D.M.)

The authors declare no conflicts of interest.

S.N.F. participated in concept, design, and article preparation. E.F. and E.A.A. participated in article preparation and editing. D.K., J.O., and D.M. participated in editing. B.C.A. participated in analysis and editing. S.P. participated in the original concept, design, article preparation, and editing.

Correspondence: Sandesh Parajuli, MD, Division of Nephrology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, 4175 MFCB, 1685 Highland Ave, Madison, WI 53705. (sparajuli@medicine.wisc.edu).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001797

Simultaneous pancreas-kidney (SPK) transplants are the most common form of pancreas transplantation and are performed in patients with diabetes and kidney failure.[1] A successful pancreas transplant restores normal glucose homeostasis, effectively eliminating the risk of severe hypoglycemia and possibly preventing or reversing the development of secondary complications of diabetes.[1-3] Pancreas transplantation is the only method that effectively restores long-term normal glucose metabolism among patients with diabetes.[4] Because of improvements in surgical technique, immunosuppression, proper donor-recipient selection, perioperative care, and graft surveillance, pancreas graft survival has significantly improved in the current era.[5,6] Progress has also been made in reducing the overall surgical complication rates of SPK transplantation, which were once among the highest of all solid organ transplants.[7,8] Recently, there has been a trend toward lower complication rates after SPK transplants.[9] However, some series report relaparotomy rates from 23% to 57%.[10-12] Challenges remain concerning medical complications such as infection and rejection rates. Pertinent to these issues are the early outcomes of the transplant, in general, and the effect of delayed graft function (DGF), in particular.

A common issue among kidney transplant-alone recipients is kidney delayed graft function (K-DGF). The utilization of marginal kidneys from deceased donors, including high Kidney Donor Profile Index (KDPI) donors, acute

kidney injury donors, donation after circulatory death (DCD) donors, and broader geographic allocation (national sharing) to expand the donor pool has led to substantially increased rates of K-DGF.[13] Based on the U.S. Renal Data System and Scientific Registry of Transplant Recipients data, the rate of deceased donor DGF was 29% between 2010 and September 2018 in kidney-only recipients.[14-16] The incidence of K-DGF from DCD was even higher at 45%.[14] Among SPK recipients, although not as high, the rate of K-DGF was approximately 8%–11% in the United States.[17]

K-DGF among SPK recipients is associated with an increased risk for pancreas graft dysfunction and failure, and an increased risk of mortality.[17-20] K-DGF among kidney-only recipients is associated with an increased risk of various negative outcomes, including graft rejection and infectious complications.[21,22] Although both infections and graft rejection episodes are common issues among transplant recipients, their association with K-DGF in SPK recipients remains inadequately studied. Based on our experience and extrapolated from data on kidney-only recipients, we hypothesized that K-DGF among SPK recipients may also be associated with an increased risk for rejection, infection, and various early posttransplant complications.[21,22]

MATERIALS AND METHODS

Population Selection and Study Design

We evaluated all adult SPK recipients who underwent SPK transplants between January 1, 2000, and December 31, 2022, at the University of Wisconsin. The exclusion criteria consisted of patients who were <18 y old at the time of the transplant, pancreas-after-kidney recipients, or pancreas transplant-alone recipients. Furthermore, we excluded recipients who experienced pancreas graft failure within 2 wk posttransplant for the primary statistical analyses. However, we included those with graft failure within 2 wk of transplantation in the subgroup analysis for some outcomes.

Recipients were divided into 2 groups based on the diagnosis of K-DGF. K-DGF was defined as a need for dialysis within the first 7 d of transplant. Outcomes of interest included risk of common infections, kidney and pancreas rejection episodes, and kidney or pancreas allograft death-censored graft failure (DCGF) within the first 12 mo posttransplant. We limited those outcomes to the first 12 mo posttransplant to better correlate DGF and early posttransplant outcomes.

Some common posttransplant infections that were considered outcomes of interest include: pneumonia, urinary tract infections (UTIs), postsurgical wound infections, infected intra-abdominal fluid collection, BK viremia, and cytomegalovirus (CMV) infection. We also looked for the need for posttransplant relaparotomy within 90 d, with subcategorization into 15–90 d. Additionally, we looked at the rate of common posttransplant complications including length of stay after transplant, readmission, and pancreatitis. We then categorized some of the outcomes based on the donor's type, type of diabetes, and induction immunosuppressive agent.

UTI was defined by clinical symptoms and positive urine culture with >100 000 colony-forming units/mL. All UTIs were treated with appropriate antibiotics. Asymptomatic UTIs were not included. Pneumonia was diagnosed based on consistent radiological findings, along with clinical symptoms and/or significantly positive sputum culture. According to molecular diagnostic testing (polymerase chain reaction [PCR]), we defined BK virus (BKV) infection as >250 copies/mL in plasma. Similarly, we defined CMV infection as >250 copies/mL in plasma. Before 2006, CMV was measured via a hybrid capture DNA assay. After 2006, quantitative CMV nucleic acid amplification PCR testing was adopted. Infected intra-abdominal infected fluid collection was defined based on positive fluid culture, or high clinical and radiological suspicion for infected fluid collection.

All rejection episodes were biopsy-proven. Pancreas DCGF was defined based on the current United Network for Organ Sharing criteria for pancreas graft failure, which include removal of the pancreas graft, reregistration for a pancreas transplant, registration for an islet transplant after receiving pancreas, or an insulin requirement, that is, ≥0.5 U/kg/d for 90 consecutive days.[23] Kidney DCGF was defined as the return to dialysis or kidney retransplantation. Allograft pancreatitis was defined as a rise in serum pancreatic enzymes (either amylase or lipase) >2 times the upper limits of normal.

This study was approved by the University of Wisconsin School of Medicine and Public Health Institutional Review Board (IRB protocol number: 2014-1072). This study followed the Declaration of Helsinki. The clinical and research activities being reported were consistent with the Principles of the Declaration of Istanbul as outlined in "The Declaration of Istanbul on Organ Trafficking and Transplant Tourism."

Surgical Technique

At our center, the donor pancreas was procured en bloc with the duodenum. The pancreas was placed intraperitoneally with a head-up and tail-down orientation. The donor pancreas was then anastomosed to the junction of the right common iliac vein and distal inferior vena cava, and to the right iliac artery. The donor's duodenum was then anastomosed to the recipient's proximal jejunum using a side-to-side anastomosis to achieve enteric drainage of pancreatic exocrine secretions. The kidney was then transplanted intraperitoneally and anastomosed to the bladder via a ureteroneocystostomy. Usually, in our center, the kidney and pancreas were placed contralaterally with the kidney on the left side and the pancreas on the right. All kidney transplant recipients had a double J uretero stent placed intraoperatively, which was removed at 3–6 wk posttransplant. In all recipients, a Foley catheter was placed intraoperatively and removed between 2 and 4 d posttransplant, regardless of kidney graft function status, including immediate graft function or K-DGF.

Immunosuppressive Protocols

Our center-specific induction immunosuppression therapy was consistent throughout the study period. Induction therapy included either a depleting agent (alemtuzumab or antithymocyte globulin) or a nondepleting agent (basiliximab). Triple immunosuppression with tacrolimus, mycophenolic acid, and prednisone taper was standard for all recipients. A few patients had early steroid withdrawal based on the immunologic risk and patient request. Maintenance immunosuppressive medications were started at 8 AM on the first-morning posttransplant if the patient could tolerate them by mouth. Doses of tacrolimus were adjusted based on trough levels, not based on the anticipation of K-DGF or the presence of K-DGF. The patients with K-DGF received similar immunosuppressive management, with a trough goal of 10–12 ng/mL

in the first 3 mo posttransplant, and 8–10 ng/mL from 3 to 12 mo.

Outcomes Monitoring and Prophylaxis Protocols

The prophylaxis for pneumocystis pneumonia was similar during the study period with patients receiving trimethoprim-sulfamethoxazole for 12 mo posttransplant with doses ranging from 160 to 800 mg 3 times a week to daily based on renal function. Recipients received prestent removal antibiotics prophylaxis with a single dose of ciprofloxacin 500 mg by mouth 2–3 h before stent removal. Alternatively, cephalexin or fosfomycin were given if the patient was not able to tolerate ciprofloxacin. Valganciclovir or acyclovir for CMV prevention for 3-6 mo was used based on donor-recipient risk stratification. Monitoring for all UTIs, pneumonia, and CMV was based on clinical signs and symptoms. Posttransplant quantitative serum BK PCR was monitored every 2 wk for the first 3 mo, monthly from 3 to 12 mo, and at the time of a for-cause kidney allograft biopsy. Pancreas biopsies were primarily performed for unexplained increases in pancreatic enzymes. We also performed a pancreas biopsy for the detection of de novo donor-specific antibodies as previously described in 2022.[24]

Treatment of pancreas rejection was based on the type and severity of rejection and was graded by the Banff criteria.[25] Acute T-cell–mediated rejection was treated with intravenous steroid pulse with or without anti-thymocyte globulin (6–12 mg/kg divided into 4–10 doses), while mixed rejection was treated with steroids, anti-thymocyte globulin, intravenous immunoglobulin, and plasmapheresis. Antibody-mediated rejection was treated with steroids, intravenous immunoglobulin, and plasmapheresis.[26] Similarly, all kidney rejection episodes were biopsy-proven. Indication and management of acute rejections were described before.[27,28] Briefly, kidney biopsies were performed mainly for cause because of unexplained rise in serum creatinine, proteinuria, or the development of de novo donor-specific antibodies. Among those with both graft dysfunctions, if feasible, we perform biopsies of both grafts.

Delayed Graft Function and Regular Clinic Follow-up

Since 2011, recipients with K-DGF were followed as outpatients in our dedicated DGF clinic. Briefly, these patients were either discharged home (if local) or to a nearby hotel with a support people and a scheduled clinic visit within 1–3 d of discharge. Visits were scheduled 3 times a week and included routine laboratory tests before each visit. If dialysis was deemed necessary, an appointment was then scheduled for dialysis in the hospital's inpatient dialysis unit that same day. If no improvement in kidney graft function was noted within 7–14 d after transplantation, a kidney transplant biopsy was performed.[29,30] Before the implementation of a dedicated DGF clinic, these recipients were managed in the hospital, with at least once a day routine laboratory tests.

We follow our SPK recipients at either the University Hospital or various outreach regional clinics. After discharge from an initial transplant admission or discharge from the K-DGF clinic, patients are typically seen at posttransplant times of 3 and 6 wk, 3, 6, 12, 18, and 24 mo, and then annually. All patients have routine laboratories completed at our center before the clinic visit. All major health events, including earlier mentioned infectious complications, are managed by our transplant team. If deemed necessary for admission, we prefer patients to be admitted to the University Hospital, especially within the first year of transplant. Even if they are admitted to outside centers, all complications are documented in our clinical database. Therefore, it is unlikely that any of the outcomes of interest would have been missed.

Statistical Analyses

Baseline characteristics were compared using chi-square tests or *t* tests, as appropriate. Bivariable and multivariable logistic regression models and Cox proportional hazards regression models were used to assess associations of DGF with the risk of infection. Because of the limited outcomes, only a few pertinent variables from the baseline characteristics were included in the multivariable analyses, which included recipient age, sex, race, history of prior transplant, and KDPI. Kaplan-Meier survival analysis was created comparing K-DGF versus no K-DGF, for some of the outcomes of interest. A P value of ≤0.05 was considered statistically significant. All analyses were conducted using Stata software (Version SE 15; StataCorp LLC, College Station, TX).

RESULTS

A total of 765 SPK recipients fulfilled our selection criteria. Of these, 85 (11.1%) developed K-DGF. Donors with K-DGF were more likely to be older, have higher KDPI, and be a DCD (Table 1). Similarly, recipients in the K-DGF group were less likely to have type 1 diabetes, and more likely to be non-White recipients, compared with the no K-DGF recipients. The median number of dialysis treatments was 3 (interquartile range [IQR], 1–5), and 27 (32%) recipients received only 1 dialysis treatment. The median length of stay after the index transplant among the K-DGF group was 13 d (IQR, 9–23 d), and no K-DGF was 9 d (IQR, 7–1 d; $P < 0.001$). Twenty-eight (32.9%) in the K-DGF group and 241 (35.4%; $P = 0.65$) were readmitted within 30 d of discharge.

Urinary Tract Infection

A total of 162 (21.2%) SPK recipients developed UTI within 15 d to 1-y posttransplant (Table 2). Nineteen (22.4%) of the recipients in the K-DGF group and 143 (21.0%) of the recipients in the no K-DGF group had UTI. The mean interval from transplant to UTI among the entire cohort was 113.7 ± 102.1 d. The mean posttransplant interval for UTI in the K-DGF group was 118.2 ± 105.6 d and 113.1 ± 102.0 d in the no K-DGF group ($P = 0.88$). K-DGF was not significantly associated with the risk of UTI in the unadjusted model (hazard ratio [HR], 1.56; 95% confidence interval [CI], 0.95-2.56; $P = 0.08$). However, after adjustment for some of the baseline characteristics, K-DGF was associated with an increased risk for UTI (adjusted HR [aHR], 1.76; 95% CI, 1.06-2.94; $P = 0.03$).

Pneumonia

A total of 39 (5.1%) SPK recipients developed pneumonia within 15 d to 1-y posttransplant (Table 2). Six (7.1%) of the recipients in the K-DGF group and 33 (4.8%) of the recipients in the no K-DGF group had pneumonia. The mean interval from transplant to pneumonia among the entire cohort was 124.7 ± 103.3 d. The mean posttransplant interval for pneumonia in the K-DGF group was 77.7 ± 66.4 d and 133.3 ± 107.2 d in the no K-DGF group ($P = 0.23$). K-DGF

TABLE 1.
Baseline characteristics

	K-DGF (n = 85)	No K-DGF (n = 680)	*P*
Donor factors			
Mean age, y	34.0 (12.8)	28.2 (12.3)	**<0.001**
Female, %	34.1	37.5	0.54
Non-White, %	10.6	9.9	0.83
Mean body mass index, kg/m^2	23.9 (3.9)	24.0 (4.4)	0.85
Cause of death: cardiovascular, %	32.9	25.0	0.12
Terminal serum creatinine, mg/dL	0.90 (0.52)	0.98 (1.05)	0.52
Mean Kidney Donor Profile Index, %	28.2 (16.9)	19.1 (16.4)	**<0.001**
Donation after circulatory death, %	50.6	13.8	**<0.001**
Immunologic factors			
cPRA > 20%, %	5.3	10.7	0.14
Mean HLA mismatch (of 6)	4.4 (1.2)	4.4 (1.2)	0.87
Previous transplant, %	8.2	6.3	0.50
Recipients factors			
Mean age, y	43.3 (9.6)	42.9 (8.8)	0.70
Female, %	37.6	39.1	0.79
Non-White, %	20.0	12.1	**0.04**
Mean body mass index, kg/m^2	25.9 (3.8)	25.4 (3.8)	0.32
Pancreas cold ischemia time, h	13.5 (4.8)	13.4 (4.3)	0.95
Kidney cold ischemia time, h	15.1 (4.8)	14.8 (4.3)	0.64
Diabetes type, %			**0.04**
Type I	77.7	87.7	
Type II/other	22.4	11.6	
Induction immunosuppression, %			0.83
Alemtuzumab	30.6	33.7	
Anti-thymocyte globulin	21.2	19.3	
Basiliximab	48.2	47.0	
Early steroid withdrawal, %	2.4	3.5	0.57
CMV high risk (D+/R–), %	25.9	27.8	0.71

Bold *P* values indicate statistical significance.
CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; K-DGF, kidney delayed graft function.

was not significantly associated with the risk of pneumonia in the unadjusted model (HR, 1.95; 95% CI, 0.80-4.78; *P* = 0.14). Even after adjustment for some of the baseline characteristics, K-DGF was not associated with the risk of pneumonia (aHR, 1.59; 95% CI, 0.63-4.05; *P* = 0.32).

Cytomegalovirus Infection

A total of 131 (17.1%) SPK recipients developed CMV within 15 d to 1-y posttransplant (Table 2). Fifteen (17.6%) of the recipients in the K-DGF group and 116 (17.1%) of the recipients in the no K-DGF group had CMV. The mean interval from transplant to CMV among the entire cohort was 160.1 ± 84.8 d, with the mean posttransplant interval for CMV being 148.0 ± 85.2 d in the K-DGF group and 161.6 ± 85.0 d in the no K-DGF group (*P* = 0.56). K-DGF was not significantly associated with the risk of CMV in the unadjusted model (HR, 1.23; 95% CI, 0.71-2.12; *P* = 0.47). Even after adjustment for some of the baseline characteristics, K-DGF was not associated with the risk of CMV (aHR, 1.14; 95% CI, 0.65-2.0; *P* = 0.64).

BKV Infection

A total of 97 (12.7%) SPK recipients developed BKV within 15 d to 1-y posttransplant (Table 2). Eight (9.4%) of the recipients in the K-DGF group and 89 (13.1%) of the recipients in the no K-DGF group developed BKV. The mean interval from transplant to BKV among the entire cohort was 132.1 ± 79.9 d, with the mean posttransplant interval for BKV being 115.3 ± 73.3 d in the K-DGF group and 133.6 ± 80.6 d in the no K-DGF group (*P* = 0.54). K-DGF was not significantly associated with the risk of BKV in the unadjusted model (HR, 0.68; 95% CI, 0.33-1.41; *P* = 0.30). Even after adjustment for some of the baseline characteristics, K-DGF was not associated with the risk of BKV (aHR, 0.67; 95% CI, 0.32-1.42; *P* = 0.30).

Surgical Wound Infections

A total of 30 (3.9%) SPK recipients developed surgical wound infections within 15 d to 1-y posttransplant (Table 2). Four (4.7%) of the recipients in the K-DGF group and 26 (3.8%) of the recipients in the no K-DGF group had this complication. The mean interval from transplant to wound infections among the entire cohort was 74.6 ± 74.1 d, with the mean posttransplant interval for wound infections being 73.1 ± 76.4 d in the K-DGF group and 84.5 ± 65.1 d in the no K-DGF group (*P* = 0.69). K-DGF was not significantly associated with a higher risk of wound infection in the unadjusted model (HR, 1.34; 95% CI, 0.46-3.93; *P* = 0.59). After adjustment for some of the baseline characteristics, K-DGF was still not associated with an increased risk for wound infection (aHR, 1.49; 95% CI, 0.49-4.48; *P* = 0.48). Results were generally similar in models limited to complications in the first 90 d (data not shown).

TABLE 2.

Risk of infections and need for laparotomy and pancreatitis

	Unadjusted		Adjusted[a]	
Complications	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
UTI (n = 162)				
No DGF (n = 143)	Reference	Reference	Reference	Reference
DGF (n = 19)	1.56 (0.95-2.56)	0.08	1.76 (1.06-2.94)	**0.03**
Pneumonia (n = 39)				
No DGF (n = 33)	Reference	Reference	Reference	Reference
DGF (n = 6)	1.95 (0.80-4.78)	0.14	1.59 (0.63-4.05)	0.32
CMV (n = 131)				
No DGF (n = 116)	Reference	Reference	Reference	Reference
DGF (n = 15)	1.23 (0.71-2.12)	0.47	1.14 (0.65-2.00)	0.64
BK (n = 97)				
No DGF (n = 89)	Reference	Reference	Reference	Reference
DGF (n = 8)	0.68 (0.33-1.41)	0.30	0.67 (0.32-1.42)	0.30
Surgical wound infection (n = 30)				
No DGF (n = 26)	Reference	Reference	Reference	Reference
DGF (n = 4)	1.34 (0.46-3.93)	0.59	1.49 (0.49-4.48)	0.48
Infected intra-abdominal fluid collection (n = 88)				
No DGF (n = 64)	Reference	Reference	Reference	Reference
DGF (n = 14)	1.95 (1.05-3.63)	**0.03**	2.14 (1.13-4.04)	**0.02**
Need for laparotomy within 0–90 d (n = 100)				
No DGF (n = 77)	Reference	Reference	Reference	Reference
DGF (n = 23)	1.90 (1.19-3.03)	**0.007**	2.07 (1.27-3.37)	**0.003**
Need for laparotomy within 15–90 d (n = 28)				
No DGF (n = 25)	Reference	Reference	Reference	Reference
DGF (n = 3)	1.33 (0.39-4.50)	0.65	1.41 (0.41-4.87)	0.58
Graft pancreatitis within 0–365 d (n = 62)				
No DGF (n = 49)	Reference	Reference	Reference	Reference
DGF (n = 13)	2.67 (1.41-5.05)	**0.003**	2.56 (1.34-4.91)	**0.004**
Graft pancreatitis within 15–365 d (n = 40)				
No DGF (n = 33)	Reference	Reference	Reference	Reference
DGF (n = 7)	2.26 (0.97-5.26)	0.06	2.08 (0.88-4.90)	0.10

Bold *P* values indicate statistical significance.

[a]Adjustment for age, sex, race, prior transplant, and KDPI.

CI, confidence interval; CMV, cytomegalovirus; DGF, delayed graft function; HR, hazard ratio; KDPI, Kidney Donor Profile Index; UTI, urinary tract infection.

Infected Intra-abdominal Fluid Collection

A total of 88 (11.5%) SPK recipients developed an infected intra-abdominal fluid collection within 15 d to 1-y posttransplant (Table 2). Fourteen (16.5%) of the recipients in the K-DGF group and 64 (9.4%) of the recipients in the no K-DGF group had this complication. The mean interval from transplant to the identification of an infected fluid collection among the entire cohort was 36.1 ± 25.3 d, with the mean posttransplant interval for identification of an intra-abdominal fluid collection being 44.9 ± 37.9 d in the K-DGF group and 34.2 ± 21.6 d in the no K-DGF group ($P = 0.18$). K-DGF was significantly associated with a higher risk of developing an infected intra-abdominal fluid collection in the unadjusted model (HR, 1.95; 95% CI, 1.05-3.63; $P = 0.03$). After adjustment for some of the baseline characteristics, K-DGF was still associated with an increased risk of developing an infected intra-abdominal fluid collection (aHR, 2.14; 95% CI, 1.13-4.04; $P = 0.02$). Results were generally similar in models limited to complications in the first 90 d (data not shown).

Need for Posttransplant Relaparotomy

We categorized the need for relaparotomy into 2 parts: within 0–90 d posttransplant and within 15–90 d posttransplant. A total of 100 (13.1%) SPK recipients needed relaparotomy within 0–90 d posttransplant (Table 2). Twenty-three (27.1%) of the recipients in the K-DGF group and 77 (11.3%) of the recipients in the no K-DGF group needed relaparotomy, with the most common indication for relaparotomy being intra-abdominal bleeding. The mean interval from transplant to relaparotomy among the entire cohort was 18.4 ± 41.6 d, with the mean posttransplant interval for laparotomy being 9.2 ± 15.3 d in the K-DGF group and 21.2 ± 46.4 d in the no K-DGF group ($P = 0.23$). Relaparotomy was significantly associated with a higher risk for K-DGF in the unadjusted model (HR, 1.90; 95% CI, 1.19-3.03; $P = 0.007$). Even after adjustment for some of the baseline characteristics, the need for relaparotomy was associated with an increased risk for K-DGF (aHR, 2.07; 95% CI, 1.27-3.37; $P = 0.003$). K-DGF and the need for relaparotomy were not associated in either the unadjusted or adjusted models when limited to 15–90 d posttransplant.

Graft Pancreatitis

We categorized pancreatitis into 2 parts: within 15–365 d posttransplant and within 0–365 d posttransplant. A total of 62 (8.1%) SPK recipients had pancreatitis 0–365 d posttransplant (Table 2). Thirteen (15.2%) of the recipients in

the K-DGF group and 49 (7.2%) of the recipients in the no K-DGF group ($P = 0.01$) had pancreatitis. K-DGF was significantly associated with a higher risk of graft pancreatitis in the unadjusted model (HR, 2.67; 95% CI, 1.41-5.05; $P = 0.003$). Even after adjustment for some of the baseline characteristics, K-DGF was associated with an increased risk for graft pancreatitis (aHR, 2.56; 95% CI, 1.34-4.91; $P = 0.004$). When limiting this outcome to 15–356 d posttransplant, K-DGF was not associated with increased risk for graft pancreatitis in either the unadjusted or adjusted model.

Pancreas Rejection

There were 82 (10.7%) SPK recipients with pancreas rejection within 15 d to 1-y posttransplant (Table 3). Of these, 39 were within 15–90 d posttransplant (7 in the K-DGF and 32 in the no K-DGF group). Fifteen (17.6%) of the recipients in the K-DGF group and 67 (9.9%) of the recipients in the no K-DGF group had pancreas graft rejection. The mean interval from transplant to pancreas rejection among the entire cohort was 116.6 ± 95.9 d, with the mean posttransplant interval for pancreas rejection being 108.7 ± 96.5 d in the K-DGF group and 118.0 ± 96.4 d in the no K-DGF group ($P = 0.74$). K-DGF was significantly associated with a higher risk of pancreas rejection in the unadjusted model (HR, 2.21; 95% CI, 1.21-4.01; $P = 0.009$). However, after adjustment for some of the baseline characteristics, K-DGF was not associated with an increased risk for pancreas rejection (aHR, 1.64; 95% CI, 0.88-3.07; $P = 0.12$).

Kidney Rejection

There were 82 (10.7%) SPK recipients with kidney rejection within 15 d to 1-y posttransplant (Table 3). Of these, 34 were within 15–90 d posttransplant (7 in the K-DGF group and 27 in the no K-DGF group). Twelve (14.1%) of the recipients in the K-DGF group and 70 (10.2%) of the recipients in the no K-DGF group had kidney rejection. The mean interval from transplant to kidney rejection in the entire cohort was 140.0 ± 111.1 d, with the mean posttransplant interval for kidney rejection being 87.7 ± 140.0 d in the K-DGF group and 149.0 ± 112.7 d in the no K-DGF group ($P = 0.07$). K-DGF was significantly associated with a higher risk of kidney rejection in the unadjusted model (HR, 2.09; 95% CI, 1.08-4.05; $P = 0.03$). Adjustment for some of the baseline characteristics attenuated this association (aHR, 1.71; 95% CI, 0.87-3.36; $P = 0.12$).

In the basiliximab induction group, 18 (5.6%) of 319 recipients in the no K-DGF group had kidney rejection compared with 23 (56.1%) of 41 recipients in the K-DGF group ($P = 0.001$). Among recipients with anti-thymocyte globulin or alemtuzumab induction group, 33 (9%) of 361 recipients in the no K-DGF group had kidney rejection compared with 8 (18%) of 44 recipients in the K-DGF group ($P = 0.36$). The rate of kidney rejection was significantly higher among K-DGF with basiliximab induction compared with the anti-thymocyte globulin or alemtuzumab induction group (56.1% versus 18%; $P < 0.001$).

Among the recipients with basiliximab induction, 25 (7.8%) of 319 recipients in the no K-DGF had pancreas rejection, compared with 16 (39%) of 41 of recipients in the K-DGF group ($P = 0.09$). In the anti-thymocyte globulin or alemtuzumab induction group, 35 (10%) of 361 recipients in the no K-DGF group had pancreas rejection compared with 6 (14%) of 44 recipients in the K-DGF group ($P = 0.90$). The rate of pancreas rejection was significantly higher among K-DGF with basiliximab induction compared with the anti-thymocyte globulin or alemtuzumab induction group (39% versus 14%; $P < 0.001$). Among the no K-DGF group, the rate of kidney rejections ($P = 0.67$) or pancreas rejection ($P = 0.77$) were not significantly different compared with basiliximab versus anti-thymocyte globulin or alemtuzumab induction group.

Pancreas Death-censored Graft Failure

There were 23 (3.0%) SPK recipients with pancreas DCGF within 15 d to 1-y posttransplant (Table 3). Of these, 12 were within 15–90 d posttransplant (5 K-DGF group and 7 in the no K-DGF group). Eight (9.4%) of the recipients in the K-DGF group and 15 (2.2%) of the recipients in the no K-DGF group had pancreas DCGF. The mean interval from transplant to

TABLE 3.

Risk for rejection episodes and graft failure

	Unadjusted		Adjusted[a]	
Complications	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Pancreas rejection (n = 82)				
No DGF (n = 67)	Reference	Reference	Reference	Reference
DGF (n = 15)	2.21 (1.21-4.01)	**0.009**	1.64 (0.88-3.07)	0.12
Kidney rejection (n = 82)				
No DGF (n = 70)	Reference	Reference	Reference	Reference
DGF (n = 12)	2.09 (1.08-4.05)	**0.03**	1.71 (0.87-3.36)	0.12
Pancreas death-censored graft failure (n = 23)				
No DGF (n = 15)	Reference	Reference	Reference	Reference
DGF (n = 8)	5.66 (2.32-13.80)	**<0.001**	4.88 (1.90-12.51)	**<0.001**
Kidney death-censored graft failure (n = 9)				
No DGF (n = 8)	Reference	Reference	Reference	Reference
DGF (n = 1)	1.40 (0.17-11.73)	0.76	1.31 (0.15-11.14)	0.80

Bold *P* values indicate statistical significance.

[a]Adjustment for age, sex, race, prior transplant, and KDPI.

CI, confidence interval; DGF, delayed graft function; HR, hazard ratio; KDPI, Kidney Donor Profile Index.

pancreas DCGF among the entire cohort was 137.0 ± 114.1 d, with the mean posttransplant interval for pancreas DCGF being 81.4 ± 89.1 d in the K-DGF group and 166.6 ± 117.4 d in the no K-DGF group ($P = 0.09$). K-DGF was significantly associated with a higher risk of pancreas DCGF in the unadjusted model (HR, 5.66; 95% CI, 2.32-13.80; $P < 0.001$). This was further confirmed by the unadjusted Kaplan-Meier survival curve (Figure 1). Even after adjustment for some of the baseline characteristics, K-DGF remained associated with an increased risk for pancreas DCGF (aHR, 4.88; 95% CI, 1.90-12.51; $P < 0.001$).

Kidney Death-censored Graft Failure

There were 9 (1.2%) SPK recipients with kidney DCGF within 15 d to 1-y posttransplant (Table 3). Of these, 2 were within 15–90 d posttransplant (both in the no K-DGF group). One (1.2%) of the recipients in the no K-DGF group and 8 (1.2%) of the recipients in the no K-DGF group had kidney DCGF. The mean interval from transplant to kidney DCGF among the entire cohort was 182.4 ± 95.6 d, with the posttransplant interval for kidney DCGF being 117 d in the K-DGF group and 183.1 ± 102.4 d in the no K-DGF group. K-DGF was not significantly associated with a higher risk of kidney DCGF in the unadjusted model (HR, 1.40; 95% CI, 0.17-11.73; $P = 0.76$). Even after adjustment for some of the baseline characteristics, K-DGF was not associated with an increased risk for kidney DCGF (aHR, 1.31; 95% CI, 0.15-11.14; $P = 0.80$).

A total of 98 SPK recipients had T2DM. Of these, 29 (29.6%) were DCD and 69 (70%; $P < 0.001$) were donation after brain death organ recipients. The rate of K-DGF was significantly higher among DCD T2DM recipients at 37.9% (11/29), compared with 24.6% (17/69; $P = 0.001$) in donation after brain death recipients.

A total of 17 pancreas grafts failed within the first 2 wk of transplant and were not included in the primary analysis. Four (23.5%) of the grafts were in the K-DGF group and 13 (76.5%) were in the no K-DGF group. Of these 17 SPK recipients with failed pancreas grafts, only 1 was the recipient of DCD organs.

DISCUSSION

In this large cohort of 765 SPK recipients, 11.1% developed K-DGF. We found K-DGF to be associated with an increased risk for various complications including UTI, infected intra-abdominal fluid collections, need for relaparotomy, graft pancreatitis, and pancreas DCGF. Although in univariable analysis risk of either kidney or pancreas graft rejection was significantly higher in the K-DGF group, this was not true after adjustment for various pertinent variables.

The association between K-DGF and risk for infections has been studied in kidney-only recipients in the past, with mixed findings. Guimarães-Souza et al[31] reported that K-DGF was linked to an increased risk of infections. In their study, the authors categorized kidney transplant recipients into 3 groups: immediate graft function (>30% decrease in serum creatinine on the second day of transplant), slow graft function (<30% decrease in serum creatinine on the second day of transplant), and K-DGF as need for dialysis within the first week of transplant. They reported slow graft function and K-DGF to have a higher rate of viral infections within 2 y of transplant at 46% for each compared with 31% among immediate graft function ($P = 0.05$).[31] The authors hypothesized that this observation could be related to some degree of immunosuppression secondary to uremic toxins, as patients with kidney disease are more susceptible to infections.[32] In 1 multicenter study among kidney transplant recipients

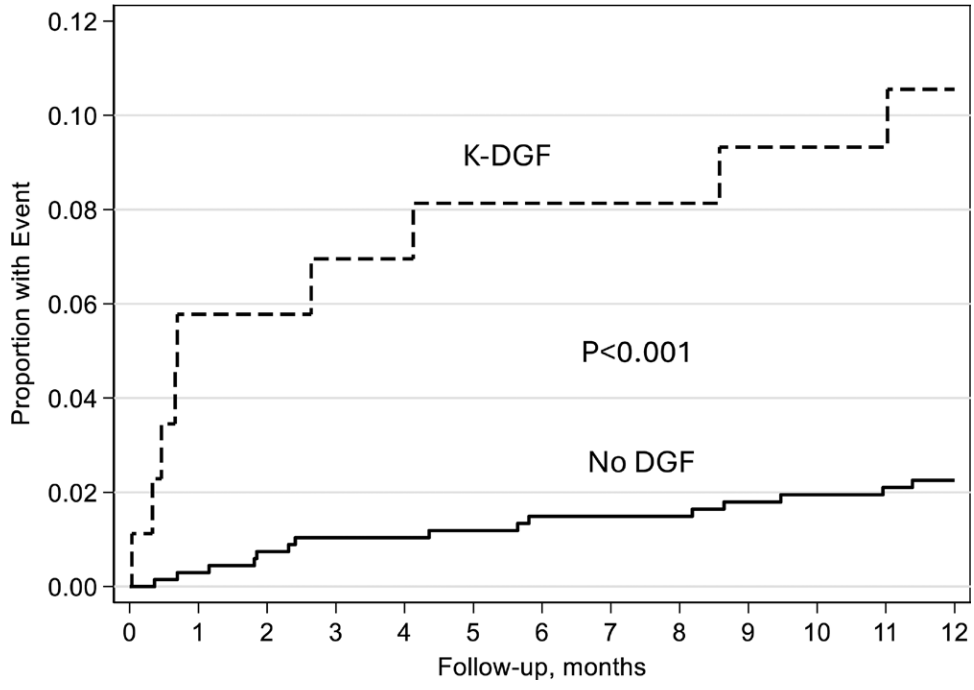

FIGURE 1. Significant increase in unadjusted Kaplan-Meier survival analysis curve for risk of pancreas death-censored graft failure in DGF compared with no DGF group ($P < 0.001$). DGF, delayed graft function; K-DGF, kidney delayed graft function.

transplanted before 1998, the authors noted an increased risk of CMV among recipients with K-DGF; however, there was no mention of CMV prophylaxis or CMV serostatus among donors and recipients.[33] Another study also suggested a correlation between K-DGF and the increased risk of CMV.[34] Even in the current era of CMV prophylaxis, Kleinherenbrink et al,[35] reported an increased risk of CMV among patients with K-DGF, along with an increased risk of CMV disease despite valganciclovir prophylaxis, possibly suggesting a suboptimal effect of prophylaxis among recipients with K-DGF. In contrast, a few studies showed no association between K-DGF and viral infection.[36-38]

Similar to our study, a few studies report a 1.5–4 times higher risk of UTI among kidney-only transplant recipients with K-DGF.[39-41] The authors hypothesized increased risk of UTI among patients with K-DGF could be related to low urine output and a poor immune system. A few studies reported an increased risk of pneumonia among kidney-only recipients with K-DGF.[42-44] Recently, our group has reported a significantly increased risk of UTI by 70% and BK viremia by 34% with K-DGF among 1512 deceased donor kidney recipients, of which 31% had K-DGF.[21] Extrapolating from the kidney-only transplant data, even among SPK recipients in this current study, we report an increased risk of infections, particularly UTIs. The correlation of K-DGF with surgical site infections has been reported in the past among kidney-only recipients but was not seen in SPK recipients in this study.[45,46] However, K-DGF was associated with an increased risk for intra-abdominal infected fluid collection. Also, K-DGF was associated with graft pancreatitis mainly in the early phase of the transplant. Although the exact pathophysiology behind this is unclear, hyperamylasemia may be pronounced with impaired graft function.[47] Also, in our study, we report associations between relaparotomy and K-DGF between postoperative days 0–90. However, when looking at risk between 15 and 90 d, K-DGF was not associated with increased risk. The most common indication for the need for early relaparotomy was intra-abdominal bleeding. Also, in this study, we report relation between K-DGF and increased risk of an infected intra-abdominal fluid collection.

K-DGF is a well-known risk factor for kidney rejection among kidney-only recipients.[22] Ischemia-reperfusion injury is a consequence of transplantation that often leads to K-DGF.[48] The reperfusion of the ischemic kidney induces a pro-inflammatory reaction in which activation of the complement system plays a central role.[49] In contrast to the kidney-only transplant recipients, in the current study, we report no significantly increased risk of kidney or pancreas rejection among SPK recipients with K-DGF, which could be associated with targeting higher immunosuppressive doses and levels. Also, in this study, we report an increased risk of kidney and pancreas rejection among SPK recipients with K-DGF receiving nondepleting induction agents. Similar to the kidney-only transplant recipients,[50] although depleting induction agents may not prevent DGF, the reduced risk of acute rejection may minimize the consequence of K-DGF among SPK recipients. Previously, we have reported K-DGF to be associated with increased risk for pancreas DCGF among SPK recipients.[18] These findings were consistent with our current report. The exact mechanisms of increased risk of pancreas DCGF with K-DGF are unknown. One of the hypotheses for pancreas DCGF in K-DGF could be because of the longer uremia time and a greater risk of bleeding in the K-DGF, fluid overload and edema around the graft, or reperfusion injury of the pancreas possibly because of an overall lower quality donor. Our findings of increased risk of pancreas graft failure were similar to the one presented by Singh and Kim,[51] where they noted a 42% increased risk of pancreas graft failure among SPK recipients with K-DGF even after the adjustment of potential confounders. Also, in 1 small study among 34 SPK recipients with K-DGF, Rangel et al[20] found a > 5-fold increased risk of death, with most deaths (>70%) occurring within the first 90 d of transplant.

This study has the expected limitations of a single-center observational study, reflecting our specific population and clinical approach. Our findings are reflective of the practices at our center, and this should be factored into the interpretation. Because of the limited number of infectious complications only a few common infections were included. Also, we were not able to provide the details of Foley catheter duration, as this data was not collected consistently. Furthermore, because of the limited sample size, it was not possible to censor the infections before rejection episodes. However, this substantial dataset with more granular data provides useful information for estimating risks and outcomes. Also, to the best of our knowledge, this study is the largest single-center study in the modern era with consistent surgical techniques and maintenance immunosuppressive agents.

In summary, K-DGF among SPK recipients was associated with multiple infections and other complications. Innate immune responses to surgery and inflammation from ischemia-perfusion injury may have contributed to this unique situation. Providers should consider the risk of various complications in the case of K-DGF among SPK recipients.

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