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ORIGINAL ARTICLE

Simultaneous pancreas-kidney transplantation in Caucasian versus African American patients: Does recipient race influence outcomes?

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Abstract

The influence of African American (AA) recipient race on outcomes following simultaneous pancreas-kidney transplantation (SPKT) is uncertain.

Methods: From 11/01 to 2/19, we retrospectively studied 158 Caucasian (C) and 57 AA patients (pts) undergoing SPKT.

Results: The AA group had fewer patients on peritoneal dialysis (30% C vs. 14% AA), more patients with longer dialysis duration (28% C vs. 51% AA), more sensitized (PRA ≥20%) patients (6% C vs. 21% AA), and more patients with pretransplant C-peptide levels ≥2.0 ng/ml (11% C vs. 35% AA, all $P < .05$). With a mean 9.2 year follow-up, patient survival (65% C vs. 77% AA, $P = .098$) slightly favored the AA group, whereas kidney (55% C vs. 60% AA) and pancreas (48% C vs. 54% AA) graft survival rates (GSRs) were comparable. Death-censored kidney (71% C vs. 68% AA) and pancreas (both 62%) GSRs demonstrated that death with a functioning graft (DWFG) was more common in C vs. AA patients (23% C vs. 12% AA, $P = .10$). The incidence of death-censored dual graft loss (usually rejection) was 7% C versus 21% AA ($P = .005$).

Conclusions: Following SPKT, AA patients are at a greater risk for dual immunological graft loss whereas C patients are at greater risk for DWFG.

KEYWORDS
African American, alemtuzumab, portal-enteric drainage, race, simultaneous pancreas-kidney transplant

1 | INTRODUCTION

Although first developed as a therapeutic modality to re-establish endogenous insulin secretion (C-peptide production) responsive to normal feedback controls (auto-regulating), vascularized pancreas transplantation (PTx) has evolved over the past several decades to complete β cell replacement that frees the patient with diabetes mellitus both from the need to monitor serum glucose and administer

exogenous insulin. A functioning PTx mitigates glycemic variability while eliminating the daily stigma and burden of diabetes in exchange for the administration of and side effects associated with chronic immunosuppression. According to the International Pancreas Transplant Registry, as of 2020, > 34 000 PTxs have been performed in the United States (US) in the past 50+ years.[1–3] Success rates for PTx have progressively improved, secondary to refinements in diagnostic and therapeutic technologies and surgical techniques, advancements in immunosuppression and anti-infective prophylaxes, new and effective techniques in organ retrieval and preservation technology, and increased experience in the selection of donors and recipients.[1–3] The vast majority of PTxs (> 80%) are performed as simultaneous pancreas-kidney transplants (SPKTs) in patients with diabetes and advanced kidney disease or kidney failure. At present, approximately 1000 PTxs are performed annually in the US including > 800 SPKTs.[1–3]

Entering the new millennium, > 95% of SPKTs were performed in patients with type 1 diabetes and 90% of recipients were Caucasian (C). However, in the past 2 decades, the annual proportion of SPKT recipients with a type 2 diabetes phenotype (detectable C-peptide levels, later age of onset and shorter duration of diabetes, not immediately insulin-requiring at time of diagnosis) has increased from 6% to 18% commensurate with an increase in the annual proportion of African American (AA) SPKT recipients from 10% to 30%.[1–3] For SPKT recipients reported as having type 1 diabetes, approximately 60% are C and 24% are AA. Conversely, for SPKT recipients reported as having type 2 diabetes, 40% are AA and 24% are C.[1–3] Nevertheless, based on population data and the incidences of insulin dependent diabetes mellitus and end stage renal disease, the proportion of SPKTs performed in AA recipients should be higher if the procedure was performed equitably in C and AA patients.[4–6] The cause of this disparity is unclear but may be related in part to differences in access, insurance status, social support networks, and perceived inferior outcomes reported in AA SPKT recipients with either type 1 or type 2 diabetes when compared to C recipients.[4–7] Because there are few recent reports in the literature on outcomes of SPKT in AA recipients,[8–20] the purpose of this study was to review retrospectively our single center experience with SPKT in the modern era (new millennium) according to recipient race in patients undergoing similar procedures and managed by standardized regimens.

2 | METHODS

2.1 | Study design

For purposes of this study, we retrospectively reviewed 220 SPKTs performed at our center from 11/01 to 2/19 (minimum 21 month follow-up) and identified 158 C, 57 AA, and five other race (three Hispanic, two Asian) recipients. We excluded the five patients who were neither non-Hispanic C nor AA race. The first AA SPKT recipient was actually #3 in our overall experience, dating back to 2/20/02. All patients received similar immunosuppression and perioperative management strategies.[21–24]

Primary outcomes were patient survival after transplantation, pancreas and kidney overall allograft survival, death-censored pancreas and kidney allograft survival, and dual death-censored graft survival. Renal allograft loss was defined as death with a functioning graft (DWFG), transplant nephrectomy, return to dialysis, or kidney retransplantation. Pancreas graft loss was defined as DWFG, allograft pancreatectomy, pancreas retransplantation, or resumption of daily insulin therapy.

2.2 | Donor and recipient selection

General indications for PTx were insulin-requiring diabetes with complications and the predicted ability to tolerate the operative procedure, manage the requisite immunosuppression, and deal with the need for close follow-up post-SPKT irrespective of C-peptide production.[21–25] Specific indications for SPKT included stage 4/5 chronic kidney disease or end stage renal disease and the absence of any contraindications. Contraindications included age > 65 years; insufficient cardiovascular reserve; current substance abuse; active infection or recent malignancy; major ongoing psychiatric illness, recent noncompliance or lack of adequate social support; significant obesity (body mass index > 32 kg/m^2); severe vascular disease; or inability to either understand or commit to the more intense follow-up associated with SPKT compared to kidney alone transplantation.[21–25] Selection criteria for SPKT in "type 2″ diabetes included patients < 60 years of age, insulin-requiring for a minimum of 3 years with a total daily insulin requirement < 1 u/kg/day, a fasting C-peptide level < 12 ng/ml, absence of severe vascular disease or tobacco abuse, adequate cardiac function (ejection fraction > 45%), and presence of "complicated" or hyperlabile diabetes.[21–25] For purposes of this study, "type 2″ diabetes was defined as having a pretransplant C-peptide level ≥ 2.0 ng/ml.

At our center, donor and recipient selection for SPKT are more stringent and conservative compared to kidney alone transplantation. In general, donor selection is restricted to donors < 40 years of age with no history of hypertension and the absence of either a cardiovascular or cerebrovascular cause of death (other than anoxic encephalopathy from cardiac arrest secondary to a drug overdose). In addition, our "tolerance" for vascular and cardiac disease in recipients is much lower for SPKT compared to kidney alone transplant candidates. In other words, we avoid patients with a history of a major amputation, low ejection fraction (< 45%), h/o multiple cardiac or cerebrovascular events, moderate to severe peripheral vascular disease, and poor functional status. There is clearly a donor and recipient selection bias for SPKT compared to kidney alone transplantation independent of race at our center.

In SPKT, the psychosocial evaluation is particularly important, given the more intensive nature of the aftercare that is required compared to kidney alone transplantation. For example, most SPKT recipients are sent home with central indwelling venous catheters for short-term fluid and electrolyte replacement and are seen in clinic follow-up twice weekly for the first 2–3 months post-transplant. Subsequent clinic follow-up by the transplant center is more frequent and for a longer duration of time (at least 1 year) compared to kidney alone recipients.

We require that patients have at least one primary caregiver available for the first 1–2 months post-transplant and have reliable transportation moving forward for frequent clinic follow-up. We rely primarily on our transplant social workers, with input from the dialysis unit nurses, social workers and referring nephrologists, as needed, to ascertain overall compliance, health literacy, and potential to manage the more stringent requirements associated with SPKT. Patients with excessive weight gain between hemodialysis sessions, missed appointments, poor control of hypertension or diabetes, or difficulty contacting the patient and scheduling tests during the pretransplant evaluation process are examples of patients who may not predictably do well with SPKT. For patients with a history of mental health or addiction issues, we require clearance from their mental health provider as part of the evaluation process.

2.3 | Technical aspects

All patients were blood type ABO compatible and T- and B-cell negative by flow cytometry crossmatch. Nearly all SPKTs were initially approached as intent-to-treat with portal-enteric drainage ($n = 192$) using an anterior approach to the superior mesenteric vein (pancreas positioned above the small bowel mesentery) and enteric exocrine drainage to the proximal ileum in the recipient (side-to-side duodenoenterostomy without a diverting Roux limb).[26] Arterial inflow was based on the recipient's right common iliac artery after the pancreas dual artery blood supply was reconstructed with a donor common iliac bifurcation "Y" graft.[26–28] In patients with unsuitable anatomy for portal-enteric drainage, systemic-enteric drainage ($n = 23$) was performed with the pancreas positioned below the mesentery with vascular anastomoses to the right common iliac artery and vein.[29] Of the first 121 SPKTs (from 11/01 to 8/10), all but two were performed by transplanting the kidney to the left iliac vessels and the pancreas to the right common or external iliac artery through a midline intraperitoneal approach. However, since 8/10, most SPKTs were performed with ipsilateral placement of the kidney and pancreas to the right iliac vessels in order to reduce operating time and to preserve the left iliac vessels for future transplantation.

2.4 | Anti-coagulation

In selected SPKT recipients, 2000–3000 units of intravenous heparin (30–50 u/kg) were administered as a single dose during surgery prior to implantation of the pancreas and a heparin infusion was continued post-transplant (continuous infusion of 300 units/h for 24 h, then 400 units/h for 24 h, and then 500 units/h until post-operative day 5) in the absence of bleeding.[30] Indications for intravenous heparin included preemptive SPKT, history of thrombophilia or clotting disorder in the recipient, small or diseased donor or recipient vessels, prolonged pancreas cold ischemia (> 16 h), extended donor criteria, or history of prior pancreas graft thrombosis. Anti-platelet therapy, consisting of oral aspirin (81 mg/day), was administered to all patients.

2.5 | Immunosuppression and post-transplant management

Patients received depleting antibody induction with either single dose alemtuzumab or multi-dose alternate day rabbit anti-thymocyte globulin (RATG, 1.5 mg/kg/dose, total 3–5 doses) in combination with tacrolimus, mycophenolate mofetil or mycophenolic acid, and tapered steroids or early steroid withdrawal.[21–25] RATG was the primary induction agent from 2001 to 2004. From 2005 through 2008, 46 SPKT patients were prospectively randomized to receive either alemtuzumab or RATG.[23,24] Since 2009, alemtuzumab has been the primary induction agent. The majority of SPKT recipients ($n = 153$) received single dose alemtuzumab induction (30 mg intravenous administered intra-operatively) in combination with tacrolimus (target 12 h trough levels 8–10 ng/ml), full dose mycophenolate (720 mg bid), and either early steroid elimination or rapid prednisone taper (dose reduction to 5 mg/day by 1 month following SPKT).[23,24] The remaining 62 patients received RATG induction with triple maintenance immunosuppression ± early steroid withdrawal. All patients received anti-infective prophylaxis with peri-operative cefazolin for surgical site prophylaxis, fluconazole for 1 month, valganciclovir for 3–6 months (6 months in patients for primary cytomegalovirus exposure, 3 months for all other patients), and trimethoprim-sulfamethoxazole long-term.[21–25] Most patients were discharged from the hospital after placement of a tunneled central venous catheter and received intravenous fluid and electrolyte supplementation at home for a variable period. Treatment of hypertension, hyperlipidemia, anemia, and other medical conditions was initiated as indicated, aiming to maintain the blood pressure < 140/90 mm Hg, fasting serum cholesterol < 200 mg/dl, and hemoglobin > 7–8 gm/dl.

2.6 | Statistical analysis

Data were compiled from both prospective and retrospective databases, with confirmation by medical record review in accordance with local Institutional Review Board guidelines and approval. Categorical data were summarized as proportions with percentages, and continuous data were summarized as means and standard deviations. Student's t test and one-way ANOVA tests were utilized to compare continuous variables according to whether the data was normally distributed. For categorical variables, the chi-square test and Fisher's exact test were utilized as appropriate to determine significance. Patient and graft survival rates (GSRs) were compared using Kaplan-Meier curves and log-rank tests. Cox multivariate regression was used to compare survival controlling for recipient characteristics including age, race, dialysis type (hemodialysis, peritoneal dialysis, preemptive), dialysis duration, calculated panel reactive antibody (PRA) level ≥20%, five or six human leukocyte antigen (HLA) mismatch (reference: 0–4 HLA mismatch), C-peptide level ≥2 ng/ml, duration of diabetes pre-transplant. Hazards ratios (HR) including 95% confidence intervals (CI) were reported for AA recipients (reference: C). Factors included in survival models were chosen a priori based on clinical significance and

secondarily according to significant differences between treatment groups defined by a *P*-value <.05.

Schoenfeld residuals tests and the Kaplan-Meier curves were utilized to assess the proportional hazards (PH) assumption. Goodness of fit was assessed according to chi-squared statistics for survival models. When evidence of time-varying effects were present violating the PH assumption, multivariate models were analyzed separately for early and late post-transplant time periods such that PH assumption was met within these time-dependent models. A two-sided *P*-value of <.05 was considered to be significant. All analyses were performed with STATA software (version 15.1, College Station, TX, USA).

3 | RESULTS

From 11/4/01 to 1/27/19, we performed 220 SPKTs at our center (minimum 22 month follow-up) and identified 158 C, 57 AA, and five other race (three Hispanic, two Asian) recipients. We excluded five patients who were neither C nor AA race. Mean follow-up was 9.4 years C versus 9.0 years AA; 92% of C and 96% of AA patients had at least 4 years follow-up (and 81% of C and 70% of AA patients had at least 8 years follow-up). Mean donor age (27 years C vs. 23 AA) and recipient age (44 years C vs. 40 AA) were both significantly older in the C group ($P \leq .02$, Table 1). Mean kidney (16.1 h) and pancreas cold ischemia (15.3 h) times were similar between groups. Recipient gender (59% C male vs. 56% AA male) was likewise similar. Additional donor and recipient characteristics for the C and AA groups are depicted in Table 1. The AA group had fewer patients on peritoneal dialysis (30% C vs. 14% AA), more patients with a longer duration (> 20 months) of dialysis (28% C vs. 51% AA), more sensitized (PRA ≥ 20% patients, 6% C vs. 21% AA), more 5–6 HLA mismatches (51% C vs. 67% AA), fewer patients who were cytomegalovirus seronegative, more patients with pretransplant C-peptide levels ≥ 2.0 ng/ml (11% C vs. 35% AA), and more patients with a shorter duration (< 20 years, 23% C vs. 47% AA) and later age of diabetes onset (≥ age 24; 13% C vs. 30% AA, all $P < .05$) compared to the C group.

Outcomes are depicted in Table 2. Overall patient survival (65% C vs. 77% AA, $P = .098$) slightly favored the AA group, whereas kidney (55% C vs. 60% AA) and pancreas (47.5% C vs. 54% AA) GSRs were comparable. The actual 8-year patient survival rate was slightly higher in the AA group (78% C vs. 90% AA, $P = .11$). Death-censored kidney (71% C vs. 68% AA) and pancreas (both 62%) GSRs demonstrated that DWFG was more common in C (23%) versus AA pts (12%, $P = .10$). Mean duration of initial hospital stay (10.0 ± 5.5 days C vs. 9.2 ± 3.7 days AA) was similar between groups. Rates of early graft loss (usually thrombosis) were 7% C versus 5% AA, rates of early relaparotomy (within 3 months of SPKT) were 36% C versus 35% AA, and 5-year cumulative clinical acute rejection rates were 27% C versus 33% AA (all P = NS).

3.1 | Survival analysis

There were no significant differences in unadjusted patient survival after transplant according to race (Figure 1) A multivariate analysis was performed adjusting for recipient age, dialysis type, dialysis duration, calculated PRA ≥20%, 5 or 6 HLA-mismatch (reference: 0–4 mismatch), C-peptide ≥2 ng/ml, duration of diabetes pretransplant, and there was again no significant differences in survival for AA compared with the reference group of C recipients (aHR = .64, 95%CI = .31–1.32). Given a lack of violation of proportional hazards during the early and late post-transplant period and a trend towards improved survival in AA after 6 years, separate multivariate models were analyzed for years 0–6 post-transplant compared with 6 years and after (Years 0–6: aHR = 1.10. 95%CI = .51–2.39 and Years 6+: aHR = .94, 95%CI = .27–3.33). There were no significant differences in kidney overall, pancreas overall, kidney death-censored, or pancreas death-censored GSRs according to unadjusted or adjusted analyses (Figures 2–5). There was a slight trend toward improved death-censored kidney and pancreas GSRs in C recipients after 4 years (Figures 4 and 5).

3.2 | Mortality

In the C group, major causes of death ($N = 56$) were cardiac (14), sepsis/infection (8), malignancy (7), unknown (6,), stroke (6), pneumonia/respiratory failure (5), motor vehicle trauma (3), drug overdose (2), renal failure (refused dialysis, 2), suicide (1), cirrhosis (1), and COVID (1). In the AA group, causes of death ($N = 13$) were cardiac (4), pneumonia (3), sepsis (3), malignancy (1), COVID (1), and one undetermined (died at home). Actual 1-, 4-, and 8-year patient survival rates were 97.5%, 92.7%, and 77%, respectively, in the C group compared to 96.5%, 94.5%, and 90% ($P = .086$ compared to C group at 8 years), respectively, in the AA group. There were only 5 deaths (8.8%) in the first 8 years post-SPKT in the AA group compared to 29 (18.4%, $P = .096$) in the C group. However, deaths occurring > 8 years post-SPKT were comparable (17% C vs. 14% AA).

Nine deaths in the C group were related to non-traditional causes (three motor vehicle trauma, two drug overdose, two refused dialysis following renal allograft failure, one suicide, and one cirrhosis). The patient who died of cirrhosis probably had unrecognized hepatitis C virus prior to transplant or developed hepatitis C virus post-transplant. She was transplanted in 2002 and died in 2004 prior to the availability of routine hepatitis C viral diagnostic testing and treatment. Of the two patients who refused dialysis following renal allograft failure, one was relatively young (age 31 at the time of transplant and age 38 at the time of death) and had been transplanted preemptively. She was adamant in her refusal to initiate dialysis in spite of multiple pleas on the part of her family members and providers. The other patient who died of renal failure was age 61 at the time of transplant (one of our older patients in this study) and had been on dialysis for 4 years (both hemodialysis and peritoneal dialysis) prior to SPKT. She was age 63 at the time of renal allograft failure but her case was complicated by multiple infections (including polyoma virus, severe cytomegalovirus infection, and osteomyelitis) as well as acute rejection. She had become deconditioned and in essence lost her will to live so her refusal to resume dialysis was understandable. The other 6 cases

TABLE 1 Donor and recipient characteristics

Mean ± SD	AA *N* = 57	C *N* = 158	*P*-value
Donor age (years)	23.0 ± 7.8	27.2 ± 11.3	.01
Donor gender: Male	35 (61.4%)	106 (67.1%)	.44
Donor Race: C	37 (64.9%)	111 (70.2%)	.70
AA	14 (24.6%)	35 (22.2%)	
Other	6 (10.5%)	12 (7.6%)	
Donor weight (kg)	68.5 ± 14.5	71.9 ± 17.1	.19
Donor body mass index (kg/m^2)	23.5 ± 3.8	24.1 ± 5.4	.44
Kidney cold ischemia (h)	15.9 ± 4.1	16.2 ± 4.1	.66
Pancreas cold ischemia (h)	15.0 ± 4.2	15.6 ± 4.1	.35
5-6 HLA-mismatch	38 (67%)	80 (51%)	.02
HLA-mismatch	5.1 ± .9	4.7 ± 1.3	.02
Calculated PRA ≥20%	12 (21%)	10 (6.3%)	.004
Cytomegalovirus Recipient negative	20 (35%)	82 (52%)	.02
Cytomegalovirus D+/R-	13 (22.8%)	50 (32%)	.21
Retransplant	3 (5.3%)	5 (3.2%)	.67
Systemic-enteric technique	9 (15.8%)	14 (8.9%)	.12
Organ import	6 (10.5%)	30 (19%)	.21
Kidney donor profile index (%)	18 ± 15	21 ± 18	.35
Recipient age	40.0 ± 9.6	44.0 ± 9.2	.02
Recipient gender: Male	32 (56%)	94 (59.5%)	.66
Recipient weight	70.8 ± 11.9	71.5 ± 13.9	.80
Recipient body mass index (kg/m^2)	24.9 ± 4.8	24.6 ± 3.4	.63
Dialysis history: Hemodialysis	40 (70.2%)	74 (46.8%)	.001
Peritoneal Dialysis	8 (14%)	47 (29.8%)	
None (preemptive)	9 (15.8%)	37 (23.4%)	
Duration of dialysis (months)	29.3 ± 23.2	24.0 ± 24.8	.08
Dialysis duration ≥ 20 months	29 (51%)	45 (28%)	.002
Duration of diabetes (years)	21.2 ± 7.4	27.8 ± 9.5	<.001
Duration of pretransplant insulin use < 20 years	27 (47.4%)	37 (23.4%)	.01
Age of onset of diabetes (years)	18 ± 10	13 ± 6.5	<.05
Diabetes onset ≥ age 24 years	17 (29.8%)	20 (13.3%)	.007
Pretransplant C-peptide ≥2.0 ng/ml	20 (35.1%)	18 (11.4%)	<.001
Time on waiting list (months)	9.8 ± 9.9	10.7 ± 11.6	.81
Alemtuzumab induction	44 (77.2%)	112 (70.9%)	.28

of non-traditional deaths represent the real-world nature of this study.

Of the six unknown deaths in the C group, most of these were probably sudden cardiac deaths but a specific cause was never documented. The seven deaths secondary to malignancy in the C group included lung cancer (3), pancreatic cancer, metastatic bladder cancer, metastatic angiosarcoma, and lymphoma. One might contend that some of these cases were at least in part immunosuppression-related. The one death secondary to malignancy in the AA group was due to pancreatic cancer. The two cases of pancreatic cancer (one in each group) involved the native pancreas and not the allograft.

3.3 | Graft loss

Causes of kidney graft loss (*N* = 71) in the C group included DWGF (36), acute/chronic rejection (17), chronic allograft nephropathy (10), acute kidney injury (2), collapsing glomerulopathy (2), thrombosis (2), polyomavirus nephropathy (1), and thrombotic microangiopathy (1). Causes of kidney graft loss (*N* = 23) in the AA group were acute/chronic rejection (9), DWFG (7), chronic allograft nephropathy (4), acute kidney injury (2), and polyomavirus nephropathy (1). Causes of pancreas graft loss (*N* = 83) in the C group included DWFG (37), acute/chronic rejection (21), thrombosis (12), insulin resistance (7), technical

TABLE 2 Outcomes according to recipient race

Mean ± SD	AA *N* = 57	C *N* = 158	*P*-value
Overall patient survival	44 (77%)	102 (64.6%)	.098
Death with functioning grafts	6 (10.5%)	25 (15.8%)	.39
Death with functioning kidney graft	7 (12.3%	36 (22.8%)	.12
Death with functioning pancreas graft	7 (12.3%)	37 (23.4%)	.086
Overall kidney graft survival	34 (59.6%)	87 (55.1%)	.64
Death-censored kidney survival	34/50 (68%)	87/122 (71.3%)	.71
Overall pancreas graft survival	31 (54.4%)	75 (47.5%)	.44
Death-censored pancreas survival	31/50 (62%)	75/121 (62%)	NS
One year patient survival	55 (96.5%)	154 (97.5%)	NS
One year kidney graft survival	54 (94.7%)	152 (96.2%)	NS
One year pancreas graft survival	52 (91.2%)	138 (87.3%)	NS
Actual 4-year patient survival	52/55 (94.5%)	136/146 (93.2%)	NS
Actual 4-year kidney survival	40/55 (72.7%)	128/146 (87.7%)	.0175
Actual 4-year pancreas survival	40/55 (72.7%)	112/146 (76.7%)	.58
Actual 8-year patient survival	36/40 (90%)	100/128 (78%)	.11
Actual 8-year kidney survival	23/40 (57.5%)	86/128 (67.2%)	.34
Actual 8-year pancreas survival	21/40 (52.5%)	72/128 (56.3%)	.72
Follow-up (months)	107 ± 55	113 ± 59	.53
Death-censored dual graft loss (excluding thrombosis)	12 (21%)	11 (7%)	.0055
Early relaparotomy (< 3 months)	20 (35.1%)	57 (36.1%)	NS
Early thrombosis (< 1 month)	3 (5.3%)	11 (7%)	NS
Days of initial hospital stay	9.6 ± 4.6	11.0 ± 6.7	.13
Acute rejection	19 (33.3%)	43 (27.2%)	NS

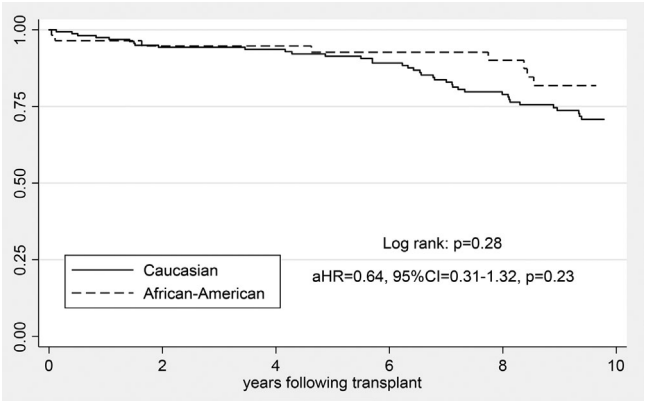

FIGURE 1 Patient survival following SPKT according to recipient race

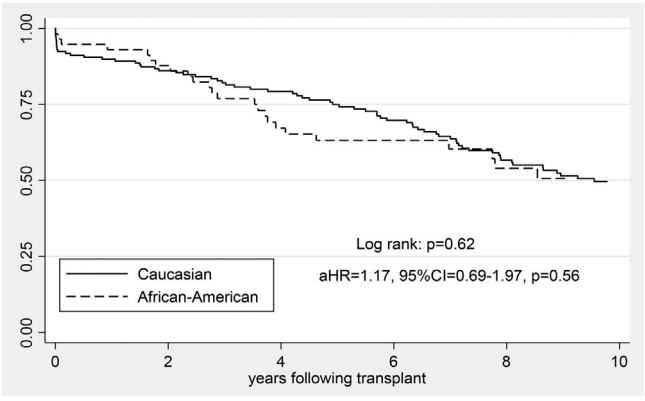

FIGURE 2 Overall kidney graft survival following SPKT according to recipient race

complications (5), and one primary nonfunction in the absence of thrombosis. Causes of pancreas graft loss (N = 26) in the AA group were acute/chronic rejection (13), DWFG (7), insulin resistance (3), and thrombosis (3). Actual one- (96.2% C vs. 94.7% AA), four- (87.7% C vs. 72.7% AA, P = .0175), and 8-year kidney GSRs (67.2% C vs. 57.5% AA, P = .34) suggested that there were more intermediate-term (1–4 years post-SPKT) kidney graft losses in the AA group and more late (> 4 years) graft losses in the C group. Actual one- (87.3% C vs. 91.2% AA), four- (76.7% C vs. 72.7% AA), and 8-year pancreas GSRs (56.2% C vs. 52.5% AA, all P = NS) were not significantly different. DWFG was the most common cause of graft loss in the C group whereas acute/chronic rejection was the most common cause of graft loss in the AA group. The incidence of death-censored dual graft loss, usually due to acute and chronic rejection, was 7% C versus 21% AA (P = .005).

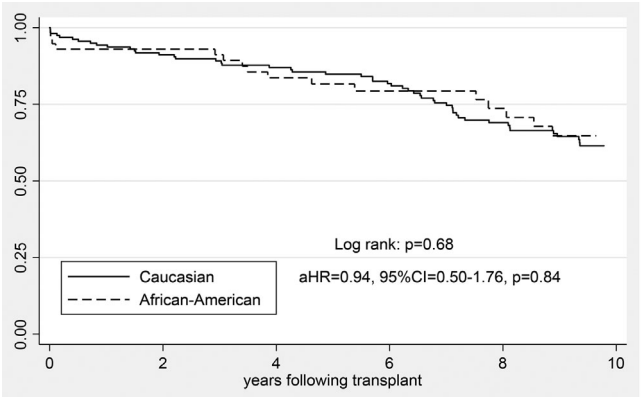

FIGURE 3 Overall pancreas graft survival following SPKT according to recipient race

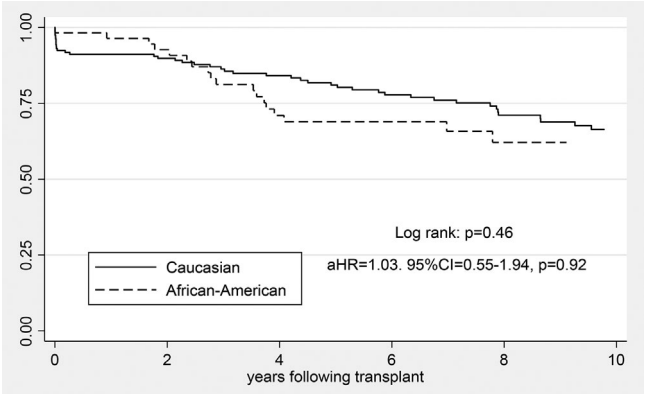

FIGURE 4 Death-censored kidney graft survival following SPKT according to recipient race

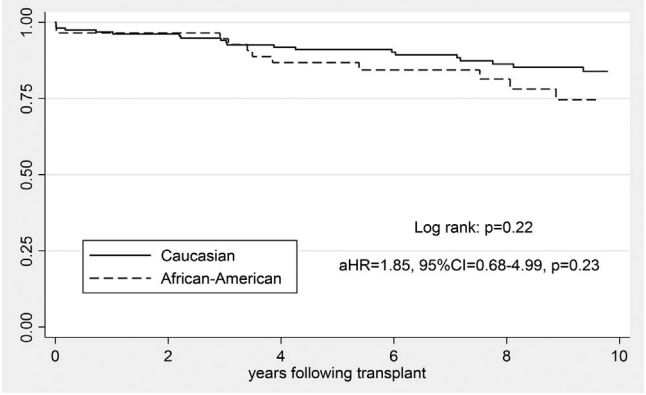

FIGURE 5 Death-censored pancreas graft survival following SPKT according to recipient race

4 | DISCUSSION

Diabetes and kidney disease remain among the top ten causes of death in the US.[31,32] The age-adjusted data for 2017–2018 indicate that the prevalence of diagnosed type 1 diabetes is higher among AA compared to C adults. In addition, previous studies have reported that AA patients with type 1 diabetes have worse metabolic control and a higher incidence of end organ damage including end stage renal disease.[33,34] There is no question that AA patients with chronic kidney disease have lower access to SPKT compared to their C counterparts, which in part may be related to referral bias secondary to perceived inferior outcomes for AA patients undergoing SPKT.[4–7] Although previous literature is conflicting, both single center and registry analyses have suggested that AA SPKT recipient may have reduced patient and GSRs compared to non-Hispanic C patients.[8–20]

There are well-documented racial differences in risk factors for kidney disease, incidence and prevalence of end stage renal disease as well as end stage diabetic nephropathy, access to kidney disease care, and health outcomes related to both kidney disease and diabetes.[4–7,35–38] Even though disparities in access to transplantation have been widely characterized, less is known about underlying mechanisms. Pervasive racial disparities persist at all levels of the renal replacement therapy process, which have been attributed to inadequate patient education and health literacy, lack of provider interest and commitment, neighborhood and health-system factors, socio-economic and insurance status, insufficient co-morbidity identification and management, and inadequate caregiver and transportation support, to name a few.[4–7] The contribution of these largely social challenges to disparities in outcomes; however, is extremely difficult to quantitate and measure and in some respects needs to be differentiated from purely biologic factors based on race. For those AA patients who are fortunate enough to be placed on the waiting list, transplant-specific disparities exist such as poor HLA-matching, longer duration of dialysis, fewer preemptive transplants, less peritoneal or home hemodialysis, heightened immunologic risks, pharmacogenomic and pharmacodynamic differences in immunosuppression, and diabetes phenotype.[4–7,35–38] Prior to consideration of patients with a type 2 diabetes phenotype, SPKT was distinctly uncommon in the AA population.

In kidney alone transplantation, AA recipient ethnicity may be associated with diminished graft survival with increased rates of acute rejection and immunologic graft loss compared to non-AA recipients.[5,6,39] In SPKT, the influence of AA race on long-term outcomes is not as well defined. One of the first registry analyses of the effect of race on outcomes following SPKT was performed by Douzdjian et al. in 1997 using registry data from the South-Eastern Organ Procurement Foundation.[8] In this study, there were no differences in actuarial patient, kidney, or pancreas GSRs at 1 and 5 years between AA and Caucasian recipients although only 12% of the patients studied were AA. In 2001 and 2005, Light et al. reviewed the Washington Hospital Center experience with SPKT in 49 AA patients with diabetes, 40% of whom were characterized as “type 2” based on C-peptide testing.[10,11] Long-term (10-year) actuarial patient, kidney, and pancreas GSRs were similar regardless of race or C-peptide status. In contrast, Rogers et al., in 2003, reported inferior outcomes in 33 AA SPKT recipients characterized by a higher incidence of acute rejection and a lower pancreas GSR compared to a concurrent control group of 63 C patients at the Medical University of South Carolina.[13] Of note, 5-year patient and kidney GSRs were comparable in this study. In a case control study, Lo et al. reported more acute rejection and lower kidney

and pancreas GSRs in 10 AA compared to 10 C SPKT recipients at the University of Tennessee-Memphis.[12]

In 2005, in an ad hoc analysis of a prospective randomized study of two dosing regimens of daclizumab induction compared to no induction in SPKT, 37 AA patients were compared to 261 non-AA patients.(15) At 3-year follow-up, there were no differences in patient, kidney, or pancreas GSRs. However, renal and pancreas allograft function and metabolic outcomes were inferior in AA recipients. In 2007 and 2009, Zhang et al. reported 5- and then 7-year outcomes in 45 AA (36 SPKT) and 73 C (55 SPKT) PTx recipients at Tulane University transplanted between 1998 and 2005.[16,17] No differences were noted in patient or GSRs although the AA group experienced a slightly higher incidence of acute rejection (cumulative incidence 36% AA vs. 31% C).

In 2010, Luan and others queried the Scientific Registry of Transplant Recipients database for all SPKTs performed between 1/1/00 and 12/31/07.[18] Of 6585 SPKTs, 931 (14.1%) were identified as AA recipients. Although there were no racial disparities in outcomes in the first 90 days post-SPKT, AA recipients subsequently experienced a 38% and 47% higher risk for late death-censored kidney and pancreas graft failure, respectively, compared to their non-AA counterparts. In addition, AA patients were twice more likely to lose either the kidney or pancreas graft secondary to rejection versus the non-AA group. In 2018, Brooks and co-authors performed a similar retrospective analysis of the UNOS database spanning 1989 through 2014.[19] Of 20 196 SPKT recipients, 15 833 (78.4%) were C, 2708 AA (13.4%), 1456 Hispanic (7.2%), and 199 Asian (1%) race. Hispanics and Asians experienced the best overall patient and GSR outcomes. Although AA patients experienced significantly superior 1-year kidney and pancreas GSRs compared to C patients, AA patients had significantly inferior patient and allograft outcomes compared to C patients beyond 3-years follow-up. In 2020, Young and associates reported their 15-year single center experience (from 1999 to 2014) at the University of Alabama-Birmingham with SPKT in 120 C and 68 AA recipients.[20] Although their results are superior to national data and the authors report "equivalent" outcomes in C versus AA SPKT recipients, their reported data actually demonstrate a 17% increased risk of death, 27% increased risk of kidney graft loss, and 15% increased risk of pancreas graft loss in AA recipients compared to the C group.

In our series ranging from 2002 to 2019, we report herein a large single center retrospective experience with SPKT in 57 AA recipients compared to a concurrent "control" group of 158 non-Hispanic C recipients. All patients received depleting antibody induction (72.5% with single dose alemtuzumab) in combination with tacrolimus/mycophenolate ± steroid maintenance immunosuppressive therapy and nearly 90% underwent PTx with portal-enteric drainage. Although no significant differences were noted in most donor and preservation variables, the C group was characterized by both older donor and recipient age. However, the AA group had significantly more patients with 5–6 HLA-mismatches, more patients with a calculated PRA level > 20%, and fewer patients who were cytomegalovirus seronegative compared to the C group. In addition, the AA group had fewer patients on peritoneal dialysis and more patients with a duration of dialysis > 20 months prior to SPKT. Duration of diabetes was shorter, age of diabetes onset was older, and presence of a C-peptide level ≥ 2 ng/ml was more common in the AA group, suggesting that a type 2 diabetes phenotype was more prevalent amongst AA recipients compared to the C group. These differences represent not only inherent biological diversity but also disparities in access secondary to psychosocial issues and implicit bias.

With a minimum follow-up of 21 months (mean 110 months), 1-year patient (97%), kidney (96%), and pancreas (88%) GSRs were excellent in both groups. Initial length of stay and the incidences of early thrombosis, relaparotomy and acute rejection were similar in both groups. However, by 4 years following SPKT, there was a slight divergence in kidney GSRs (higher in the C group, particularly in the death-censored analysis). Acute/chronic rejection was the most common cause of graft loss in the AA group, which appeared to be more prone to intermediate-term (2–4 years post-SPKT) immunologic graft loss, particularly for the kidney. The incidence of death-censored dual graft loss, usually due to acute and chronic rejection, was three times higher in the AA group. One might speculate that this finding could be related to either loss of Medicare coverage for immunosuppressant medications at 3 years, lack of close follow-up with the transplant center, or a greater intrinsic risk for immunological graft loss in the AA group. Interestingly, by 8 years following SPKT, there was a slight variation in patient survival (favoring the AA group). Mortality in the first 8 years post-SPKT as well as DWFG were both twice as likely to occur in the C group compared to the AA group. However, the late mortality rate (> 8 years post-SPKT) was similar in the two groups. Consequently, DWFG was the most common cause of graft loss in the C group and the most common causes of death were cardiac, respiratory, infection, malignancy, or stroke. However, a number of deaths in the C group were secondary to non-traditional causes, which may be related to random events rather than any true racial differences. Alternatively, perhaps our AA patients have to reach a higher bar both psychosocially and medically secondary to implicit bias, which would place them at lower risk for non-traditional deaths. Although long-term kidney and pancreas GSRs were comparable in C and AA patients, the divergent timelines and disparate causes of graft loss may have important implications on how to improve long-term outcomes and manage these racial groups going forward.

CONFLICT OF INTERESTS

None of the others authors have any conflicts of interest to disclose pursuant to this study.

DATA AVAILABILITY STATEMENT

Data available on request from the authors due to privacy/ethical issues.

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