Received: 1 October 2019 | Revised: 22 November 2019 | Accepted: 6 December 2019

DOI: 10.1111/ctr.13775

ORIGINAL ARTICLE

Clinical TRANSPLANTATION The Journal of Clinical and Translational Research WILEY

Outcomes of kidney transplantation using deceased donors with history of diabetes

Faiza N. Khan[1,2,3] | Luan D. Truong[4] | Duc T. Nguyen[5] | Edward A. Graviss[5] | Muhammad I. Bhatti[1] | Adaani E. Frost[5] | A. Osama Gaber[6,7] | Wadi N. Suki[2,3]

[1]Department of Medicine, Baylor Scott and White Hospital, Temple, Texas

[2]Nephrology Division, Department of Medicine, Weil Cornell Medical College, Houston, Texas

[3]Houston Methodist Institute for Academic Medicine, Houston, Texas

[4]Department of Pathology and Genomic Medicine, Weil Cornell Medical College, Houston, Texas

[5]Houston Methodist Research Institute, Weil Cornell Medical College, Houston, Texas

[6]Department of Surgery, J.C. Walter Transplant Center, Weil Cornell Medical College, Houston, Texas

[7]The Houston Methodist Hospital, Weil Cornell Medical College, Houston, Texas

Correspondence
Faiza N. Khan, Nephrology Division, Department of Medicine, Baylor Scott and White Hospital, Temple, TX.
Email: Faiza.Khan@BSWHealth.org

Abstract

Deceased diabetic kidneys are increasingly utilized in transplantation. The relationship of donor's history of diabetes to clinical and histological outcomes was examined. Forty-nine diabetic deceased donor kidneys (D-DM) were transplanted into 26 normal (R-N/D-DM) and 23 diabetic recipients (R-DM/D-DM) and compared to 211 diabetic recipients of normal kidneys(R-DM/D-N) and 466 normal recipients of normal kidneys (R-N/D-N). Patient survival at 5 years was 89.7% in R-N/D-N, 96.2% in R-N/D-DM, 80.1% in R-DM/D-N, and a 71.6% in R-DM/D-DM (P = .008). Death-censored graft survival at 5 years was 86.3% in R-N/D-N, 87.4% in R-N/D-DM, 93.5% in R-DM/D-N, and 87.5% in R-DM/D-DM (P = .24). Multivariable regression analysis showed that compared to non-diabetic recipients, diabetic recipients had a 2- to 3-fold increased risk of mortality. In this cohort, there was no impact on death-censored graft survival of diabetic donor status. Only 6 of 26 post-perfusion biopsies showed evidence of diabetic nephropathy (<IIa), and on repeat biopsies 70% showed no evidence of progression. Survival of recipients of diabetic donor kidneys appears dependent on the diabetic status of the recipient with the worst survival being in diabetic recipients of a diabetic donor kidney. In this cohort, donor kidneys had paucity of structural diabetic lesions and most did not show progression.

KEYWORDS

diabetes, donors and donation: deceased, kidney (allograft) function/dysfunction

1 | INTRODUCTION

The survival benefit that end-stage renal disease (ESRD) patients derive from kidney transplantation has led to an increased demand for donor kidneys. As a result, utilization of kidneys from deceased diabetic donors has emerged in the last two decades as a possible solution to this shortage.[1,2] Although deceased diabetic donor kidneys are routinely used in several centers, few studies evaluating this practice have been published. Ahmad et al noted similar patient survival, but slightly inferior graft survival in recipients of deceased diabetic donor kidneys when compared to recipients of deceased non-diabetic donor kidneys. Due to the small absolute difference, the authors concluded that diabetic donors could be used to expand the donor pool.[3] In 2012, Mohan et al demonstrated that donor diabetes did not have a significant effect on graft and patient survival and even suggested that diabetic donor kidneys may be superior to using extended criteria donor kidney.[4] Recently, Cohen et al reported discordant recipient pair analysis of diabetic donor kidneys, using United Network of Organ Sharing data, and found that although a risk was associated with diabetic donor kidneys, it was dependent on recipient diabetes status.[5]

In 1983, Abouna[6] transplanted a deceased diabetic donor kidney with histological evidence of diabetic nephropathy into a

non-diabetic recipient. A repeat biopsy 7 months afterward showed resolution of basement membrane thickening, mesangial matrix expansion, and diffuse glomerulosclerosis. Although other single case reports have been published showing reversal of diabetic lesions once euglycemia was restored, larger histological studies examining the interplay of recipient's diabetes status, pre-, and post-transplantation on deceased diabetic donor kidneys have not been reported. We, therefore, examined the relationship of recipient diabetic status and donor diabetic history to clinical and histological outcomes of kidney transplantation at our institution.

2 | MATERIALS AND METHODS

The aims of this study were as follows: (a) to compare clinical outcomes of kidney transplants from donors with or without a history of diabetes into diabetic or non-diabetic recipients; (b) to describe the histologic findings in post-perfusion biopsies in kidneys from donors with a history of diabetes; (c) to examine histologic changes following transplantation in kidneys from donors with a diabetic history. Approval for this retrospective review was obtained from the Houston Methodist Institutional Review Board.

For the first aim, retrospective analysis of electronic medical records of recipients of deceased donor kidney transplants at Houston Methodist JC Walter Jr Transplant Center between 1/2006 and 12/2014 was performed with follow-up through May 1, 2016. All recipients of deceased donor kidney transplants were further stratified into four groups based on recipient (R) and donor (D) diabetes history status (DM vs No DM history [N]). The groups were R-DM/D-DM, R- N/D- DM, R- DM/D-N, and R-N/D-N. Recipient and donor characteristics, and peri-transplant factors were analyzed. Donor characteristics such as diabetes history, race, donor age, and BMI were obtained from the United Network of Organ Sharing (UNOS) dataset. All transplant candidates at this center undergo electrocardiogram, echocardiogram, stress test, and cardiology consultation. No patients were listed with evidence of myocardial ischemia, or heart failure or markedly reduced LVEF attributable to coronary artery disease. The primary outcomes in the study were recipient survival and death-censored allograft survival. Recipient survival and death-censored allograft survival were verified in the SRTR (Scientific Registry of Transplant Recipients) database. The criterion for accepting a kidney from a donor with a diabetic history at this center is the absence of high-grade proteinuria (>2+).

For the second and third aims, post-perfusion biopsies and subsequent "for indication" biopsies were examined and reviewed. The rate of post-reperfusion biopsies at this center is approximately 50%. Systematic examination of these biopsies, including electron microscopy (EM), was performed with special attention to features of diabetic nephropathy (DN). The diabetic changes were graded on a scale of 0-IV, as defined by the Renal Pathology Society (RPS): 0 = no diabetic changes by light microscopy (LM) or EM; I = no obvious LM changes, but thickening of glomerular basement membrane by EM; IIa = mild mesangial expansion by LM; IIb = marked mesangial expansion by LM; III = nodular mesangial sclerosis, and IV = advanced diabetic glomerulosclerosis.

Pre-existing history of diabetes or new-onset diabetes after transplantation in recipients was defined by the American Diabetic Association[7] criteria: Diabetes was defined as a fasting blood sugar ≥126 on two separate occasions or a HgbA1C ≥6.5%. New-onset diabetes after transplantation (NODAT) was defined by similar criteria or the presence of antidiabetic agents 3 months after transplantation. The time in days that a kidney resided in a "hyperglycemic environment" was calculated from the time of transplantation in diabetic recipients or from the time of onset of NODAT. Recipient's estimated glomerular filtration rate (eGFR) was calculated from the most recent serum creatinine, age, and gender using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Equation [8] Patient and graft functioning status was obtained from the SRTR STAR file. For patients marked as lost to follow-up, most recent vital status was used in the analysis and censored at the last date of follow-up.

Post-perfusion biopsies in our transplant program are undertaken to address concerns about the status of the transplanted kidneys, including abnormal renal function developing around the time of transplantation; technically complicated surgical procedures; abnormal perioperative findings of the graft; or history of donor diseases that may impair renal function but by themselves not cause donor rejection such as hypertension or diabetes. Subsequent follow-up biopsies were performed for indication such as: the development of proteinuria, worsening graft function, or the development of donor-specific antibodies (DSA).

2.1 | Statistical analysis

Baseline data were reported as medians and interquartile ranges (IQR) for continuous variables, and as frequencies and proportions for categorical variables. Differences in baseline data across groups were compared using the chi-square test for categorical variables and a Kruskal-Wallis test for continuous variables.

Patient survival was estimated using Kaplan-Meier statistics. Univariate and multivariate Cox proportional-hazards models were used to determine the contribution of potential prognostic variables to the patient outcome. Multivariate Cox proportional-hazards models were fitted using the Bayesian model averaging (BMA) methods in order to identify significant risk factors for death within 5-year post-transplant.[9,10] Briefly, Stata's BMA program was run to evaluate possible model sets from all variables evaluated in the univariate analysis. The BMA program suggested good initial models which included the variables with a high probability of being a risk factor. The Likelihood Ratio test was used to further reduce the model subsets. The best final model was selected based on the smallest Bayesian information criterion (BIC). The model's discrimination was determined by calculating the Harrell's C statistic. All analyses were performed on Stata version 15.1 (StataCorp LLC). A *P*-value of <.05 was considered statistically significant.

3 | RESULTS

Of 706 primary renal transplants, subcategories included the following: R-DM/D-DM 23, R-N/D-DM 26, R-DM/D-N 21,1 and R-N/D-N 446 patients,

3.1 | Aim 1: Patient population and outcomes

3.1.1 | Population characteristics

Of 706 recipients with deceased donor kidney transplants, 49 recipients (6.9%) received a kidney from a donor with diabetic history. Of non-diabetic recipients in the present cohort, 5.5% received a kidney from a donor with a diabetic history, and of the diabetic recipients 9.8% received a kidney from a donor with a history of diabetes. Of these 49 kidneys from donors with a diabetic history, 23 (47%) were implanted in diabetic recipients and 26 (53%) were implanted in non-diabetic recipients.

Analysis of differences between groups as shown in Table 1 revealed that the R-N/D-N group had the least proportion of males, the lowest mean age, the lowest BMI, the highest prevalence of glomerulonephritis, and polycystic kidney disease as indication for transplantation, and the lowest median donor age and donor BMI. By contrast, diabetic recipients had the highest BMI and percentage of males and Hispanics. Hypertension in the donor was most prevalent in the donors with a diabetic history. There were no significant between-group differences in dialysis vintage.

3.2 | Patient and allograft outcome

Median follow-up for the primary analysis was 50 months (95% CI 51, 57). In the entire cohort, 5-year patient and death-censored graft survival were 86.5% and 88.5%, respectively.

Kaplan-Meier analysis of patient survival at 5 years by subgroup was 89.7% in R-N/D-N, 96.2% in R-N/D-DM, 80.0% in R-DM/D-N, and 71.6% in R-DM/D-DM (Figure 1A, overall log-rank test P = .008). Of the five deaths in the latter group, three were attributable to cardiovascular disease, one attributable to PTLD refractory to therapy, and one due to graft failure with refusal to initiate dialysis.

Kaplan-Meier analysis of death-censored graft survival at 5 years by subgroup was 86.3% in R-N/D-N, 87.4% in R-N/D-DM, 93.5% in R-DM/D-N, and 87.5% in R-DM/D-DM (Figure 1B, P = .24).

3.3 | Multivariate analysis of patient and graft survival

On multivariate analysis of patient survival, diabetes status of the recipient was associated with an increase in patient mortality. Compared to control (R-N/D-N), the R-DM/D-N subgroup had nearly a twofold higher patient mortality at 5 years (HR 1.99, P = .017). Risk to a diabetic recipient was greater still, at 3-fold higher patient mortality at 5 years, with receipt of a kidney from a donor with diabetic history (R-DM/D-DM HR 3.14, P = .034) (Table 2). Age greater than 65 and dialysis vintage were associated with an increase in patient mortality at 1, 3, and 5 years.

By multivariate analysis, there was no statistically significant impact of donor diabetic history or recipient diabetes status on death-censored graft survival. However, recipient Black race, dialysis vintage, cPRAp as a continuous variable, and donor age ≥50 years were associated with poorer graft survival at 5 years. (Table 3).

3.4 | Aim # 2: Post-perfusion renal transplant biopsy findings

Of the 49 kidneys from deceased donors with diabetic history transplanted, post-perfusion biopsy was performed in 26 cases (53%) (Figure 2). Twenty cases did not exhibit evidence of diabetic nephropathy even after EM examination (Table 4). One biopsy showed thickened glomerular basement membrane by EM, but did not have any evidence of DN on light microscopy. Five biopsies showed class IIa DN characterized by mild mesangial sclerosis, hypercellularity, and thickened glomerular basement membrane. Diabetic nephropathy of higher severity (class IIb-IV) was not seen in any biopsy. Other lesions noted include arterionephrosclerosis (10/26 biopsies, 40%), interstitial fibrosis and tubular atrophy (IFTA) <15% (8 biopsies; 30%), acute tubular necrosis (4 biopsies), myoglobin casts (2 biopsies), incidental IgA nephropathy (1 biopsy), and incidental rare glomerular capillary thrombi perhaps related to organ preservation (1 biopsy).

Of the 26 post-perfusion biopsies, duration of diabetic history in the donor was unknown in seven cases, 1-5 years in nine, 6-10 years in seven, and greater than 10 years in two. Two kidneys were from the same donor. No correlation could be found between the duration of donor diabetic history and the severity of diabetic nephropathy lesions observed (Table 4).

3.5 | Aim #3: Follow-up biopsy findings

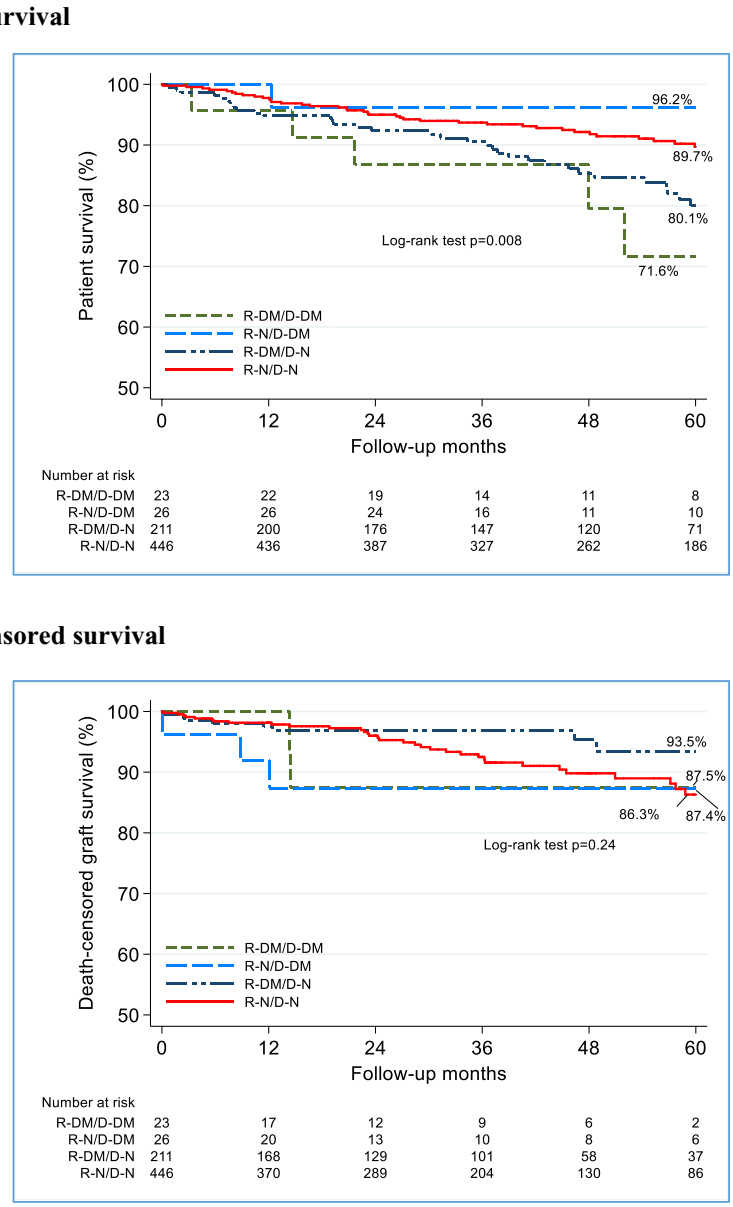
Of the 26 post-perfusion biopsies, follow-up biopsies were performed for indication (delayed graft function, elevated proteinuria, and/or presence of donor-specific antibodies) in 17 recipients (Figure 2). A total of 38 follow-up biopsies (2.2 biopsies per patient) were examined for evolution of diabetic lesions. Median time post-transplantation for the follow-up biopsies was 562 days. Progression of diabetic nephropathy was noted in 2 recipients both of whom were diabetic. Of the 20 patients with no DN on post-perfusion biopsy, 12 were rebiopsied, nine continued to show no evidence of DN, and three developed de novo DN (all three of whom were

TABLE 1 Baseline characteristics

	Total	R-DM/ D-DM	R-N/D-DM	R-DM/D-N	R-N/D-N	
	(N = 706)	(n = 23)	(n = 26)	(n = 211)	(n = 446)	*P*-value
Age at transplant (years), median (IQR)	52.0 (42.0, 61.0)	60.0 (52.0, 65.0)	58.0 (49.0, 66.0)	57.0 (48.0, 64.0)	48.0 (38.0, 58.0)	<.001
Male gender	403 (57.1)	16 (69.6)	15 (57.7)	138 (65.4)	234 (52.5)	.01
Race/Ethnicity						
White	252 (35.7)	5 (21.7)	11 (42.3)	69 (32.7)	167 (37.4)	.28
Black	235 (33.3)	10 (43.5)	9 (34.6)	61 (28.9)	155 (34.8)	.34
Hispanic	151 (21.4)	6 (26.1)	4 (15.4)	66 (31.3)	75 (16.8)	<.001
Asian	66 (9.3)	2 (8.7)	2 (7.7)	14 (6.6)	48 (10.8)	.39
Other	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)	.93
Retransplant	57 (8.1)	2 (8.7)	1 (3.8)	16 (7.6)	38 (8.5)	.84
Body mass index, median (IQR)	27.2 (23.6, 30.9)	29.8 (27.9, 31.9)	27.3 (25.2, 30.1)	28.8 (25.1, 32.2)	26.0 (22.7, 29.4)	<.001
Indication for transplant						
Hypertension only	304 (43.1)	8 (34.8)	15 (57.7)	65 (30.8)	216 (48.4)	<.001
Diabetes only	109 (15.4)	9 (39.1)	0 (0.0)	100 (47.4)	0 (0.0)	<.001
Hypertension and diabetes	17 (2.4)	4 (17.4)	0 (0.0)	13 (6.2)	0 (0.0)	<.001
Glomerulonephritis	95 (13.5)	0 (0.0)	3 (11.5)	10 (4.7)	82 (18.4)	<.001
Polycystic kidney disease	58 (8.2)	0 (0.0)	2 (7.7)	4 (1.9)	52 (11.7)	<.001
Others	123 (17.4)	2 (8.7)	6 (23.1)	19 (9.0)	96 (21.5)	<.001
Pre-tx history of hypertension	661 (94.7)	21 (91.3)	24 (96.0)	207 (98.1)	409 (93.2)	.057
Pre-tx history of diabetes	234 (33.5)	23 (100.0)	0 (0.0)	211 (100.0)	0 (0.0)	<.001
Pre-emptive transplant	65 (9.2)	1 (4.3)	1 (3.8)	18 (8.5)	45 (10.1)	.56
Dialysis duration (y), median (IQR)	3.5 (2.0, 5.0)	3.0 (2.5, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	3.5 (2.0, 6.0)	.055
cPRAp, median (IQR)	20.0 (0.0, 67.0)	3.0 (0.0, 46.0)	2.5 (0.0, 61.0)	16.0 (0.0, 70.0)	24.0 (0.0, 66.0)	.17
cPRAp ≥ 20%	356 (50.4)	8 (34.8)	10 (38.5)	102 (48.3)	236 (52.9)	0.16
cPRAp ≥ 80%	138 (19.5)	4 (17.4)	1 (3.8)	46 (21.8)	87 (19.5)	.19
Donor age, median (IQR)	38.0 (22.0, 50.0)	47.0 (42.0, 60.0)	45.0 (31.0, 54.0)	41.0 (23.0, 53.0)	34.0 (21.0, 49.0)	<.001
Donor male gender	423 (59.9)	13 (56.5)	9 (34.6)	131 (62.1)	270 (60.5)	.057
Donor race/ethnicity						
White	360 (51.0)	7 (30.4)	12 (46.2)	115 (54.5)	226 (50.7)	.16
Black	113 (16.0)	2 (8.7)	2 (7.7)	34 (16.1)	75 (16.8)	.48
Hispanic	214 (30.3)	13 (56.5)	12 (46.2)	59 (28.0)	130 (29.1)	.01
Asian	16 (2.3)	1 (4.3)	0 (0.0)	3 (1.4)	12 (2.7)	.55
Other	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	.62
Donor body mass index, median (IQR)	26.3 (22.8, 31.1)	26.8 (24.2, 38.8)	30.2 (24.2, 38.8)	26.8 (23.7, 31.1)	25.9 (22.1, 30.4)	<.001
History of hypertension, donor	166 (23.5)	14 (60.9)	14 (53.8)	46 (21.8)	92 (20.6)	<.001
History of diabetes, donor	49 (6.9)	23 (100.0)	26 (100.0)	0 (0.0)	0 (0.0)	<.001

Abbreviations: cPRAp, peak calculated panel reactive antibody; D, donor; DM, diabetes; N, normal or non-diabetic; pre-tx, pre-transplant; R, recipient; R-DM/D-DM, diabetic recipient who received a kidney from a diabetic donor; R-DM/D-N, diabetic recipient who received a kidney from a non-diabetic donor; R-N/D-DM, non-diabetic recipient who received a kidney from a diabetic donor; R-N/D-N, non-diabetic recipient who received a kidney from a non-diabetic donor.

FIGURE 1 Kaplan-Meier curves for 5-y patient and death-censored graft survival. A, Patient survival. B, Death-censored survival



diabetic; HgbA1c's 6.5, 7.0, and 10.8) In all patients with progressive or de novo DN, diabetes was present post-transplant. Recipients with progressive or de novo diabetic nephropathy had longer exposure to a hyperglycemic milieu (743 days vs 283 days) and the biopsies were obtained later in the post-transplant period (784 days vs 440 days).

4 | DISCUSSION

This is the first study to analyze the complex relationship between donor and recipient's diabetes status pre- and post-transplantation in the context of both clinical and histological data. This study suggests that (a) recipient's diabetes status has the greatest impact and adverse effect on mortality and graft survival, and (b) kidneys from donors with a history of diabetes selected for transplantation at this center have no or mild histological diabetic changes.

Patient survival at 5 years in the present cohort (706 pts; 86.5%) was comparable to that reported in the 2015 SRTR/OPTN annual report (86.3%). However, 5-year death-censored graft survival was 88.5% despite the fact that 6.9% of the kidneys transplanted came from donors with a history of diabetes.

Kidneys from donors with a diabetic history did as well as normal kidneys when transplanted into non-diabetic recipients. However, patient survival in non-diabetic recipients of kidneys from donors without a diabetic history was inferior to that of non-diabetic recipients of kidneys from donors with a diabetic history (89.7% and 96.2% 5-year patient survival, respectively). This finding may reflect the higher proportion of females (47.5% vs 42.3%, P = .01), re-transplants (8.5% vs 3.9%, P = .89), and a nearly fivefold higher proportion of recipients with a cPRAp >80% (19.6% vs 3.9%, P = .046) in the R-N/D-N than in the R-N/D-DM cohort. Other factors that may have contributed to this discrepancy in patient survival include longer dialysis vintage (a known

TABLE 2 Characteristics associated with patient mortality at 5 years, multivariable Cox proportional hazard model

	Adjusted HR (95% CI)	*P*-value
Group		
Group 1 (R-DM/D-DM)	3.14 (1.09, 9.04)	.03
Group 2 (R-N/D-DM)	0.58 (0.08, 4.33)	.59
Group 3 (R-DM/D-N)	1.99 (1.13, 3.49)	.02
Group 4 (R-N/D-N)	(reference)	
Age ≥65 years	2.19 (1.25, 3.84)	.01
Body mass index ≥30	0.77 (0.43, 1.37)	.37
Dialysis vintage, y	1.13 (1.06, 1.21)	<.001
Most recent eGFR <60 (mL/min/1.73 m^2)	2.10 (0.99, 4.48)	.053
Donor body mass index ≥30	0.57 (0.30, 1.07)	.08

Abbreviations: D, donor; DM, diabetes; eGFR, estimated glomerular filtration rate (using the using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation); R, recipient.

TABLE 3 Characteristics associated with death-censored graft loss at 5 y, multivariable Cox proportional hazard model

	Adjusted HR (95% CI)	*P*-value
Group		
Group 1 (R-DM/D-DM)	1.54 (0.36, 6.63)	.56
Group 2 (R-N/D-DM)	2.85 (0.80, 10.15)	.11
Group 3 (R-DM/D-N)	0.66 (0.28, 1.58)	.36
Group 4 (R-N/D-N)	(reference)	
Age ≥65 y	0.42 (0.12, 1.49)	.18
Black	2.50 (1.27, 4.91)	.01
Female	1.29 (0.60, 2.78)	.52
Body mass index ≥ 30	1.26 (0.61, 2.62)	.53
Most recent eGFR < 60 (mL/mn/1.73 m^2)	1.08 (0.48, 2.44)	.86
Donor body mass index ≥ 30	1.06 (0.53, 2.14)	.86
Number of kidney transplant	0.58 (0.19, 1.77)	.34
cPRAp	1.02 (1.01, 1.03)	.001
Donor age ≥50	2.13 (1.07, 4.23)	.03

Abbreviations: cPRAp, peak calculated panel reactive antibody; D, donor; DM, diabetes; eGFR, estimated glomerular filtration rate (using the using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation); R, recipient.

risk factor for all-cause mortality[11]), as well as a higher proportion of recipients with glomerulonephritis in the R-N/D-N group. Recent studies indicate recurrence of glomerulonephritis as the second leading cause of graft loss.[12]

Patient survival was lower in diabetic recipients than in non-diabetic recipients, but the survival was poorest in diabetic recipients of kidneys from donors with a diabetic history (R-DM/D-DM; 71.6%) compared to 80% survival in diabetic recipients of kidneys from donors with no diabetic history. R-DM/D-DM had the lowest patient survival of all four groups.

The development of diabetic nephropathy in a diabetic environment in the transplant setting is accelerated (6.68-5.9 years for evidence of recurrent or de novo DN, respectively, in the transplanted kidney).[13] This acceleration of pre-existing diabetic lesions may well contribute to graft failure and consequent patient death in this latter group (R-DM/ D-DM).

The better death-censored graft survival in the group of diabetic recipients of the kidneys from donors with no diabetic history (R-DM/D-N) compared to the group of non-diabetic recipients of donors with no diabetic history (R-N/D-N) may have been related to the higher patient mortality in the R-DM/D-N group (20%) compared to the R-N/D-N group (10.3%). A similar explanation may be applicable to the apparently good death-censored graft survival of the R-DM/D-DM group recipient, wherein patient survival at 5 years was only 71.6%.

Consistent with prior reports,[5] the risk associated with receipt of a kidney from a donor with a diabetic history appears to be dependent on the diabetes status of the recipient. On multivariate analysis, a nearly 2-fold increase in patient mortality was noted when diabetic recipients were compared to non-diabetic recipients.

Diabetic recipients experience higher mortality due to both an increased risk of infection, sepsis, and micro- and macrovascular disease. Theoretic rationales have been proposed to explain a potential adverse impact of diabetes on graft survival, including an increase in alloreactive T cells in diabetic recipients leading to higher rates of rejection. However, in the present cohort while an adverse impact on death-censored graft outcome in diabetic recipients was not observed increased rejection could have contributed to the higher mortality rate seen in the two diabetic recipient groups.[14]

Histological examination of post-perfusion biopsies showed either absent or mild diabetic lesions (only 6 of 26 immediate post-perfusion biopsies showed early diabetic changes). Furthermore, only 29% (5 of 17 patients with follow-up biopsies) showed evidence of histologic progression of diabetic lesions. Other papers have suggested up to 75% development of DN lesions in diabetic recipients of kidneys from donors with no diabetic history at 5-6 years post-transplant.[13] Given these clinical outcomes and the paucity of significant histological findings, one can speculate that despite any potential risk associated with a history of diabetes in the donor, the recipient's diabetes status has the greatest adverse effect on mortality.

The Kidney Donor Profile Index (KDPI) includes diabetes and hypertension as risk factors predictive of poorer graft outcome.[15] Histological examination of kidneys from donors with a diabetic history in the present study suggests that the main cause of pre-transplant renal injury was due to donor-derived microvascular disease from a combination of both hypertension and diabetes. Despite the paucity of structural damage from diabetes, arterionephrosclerosis

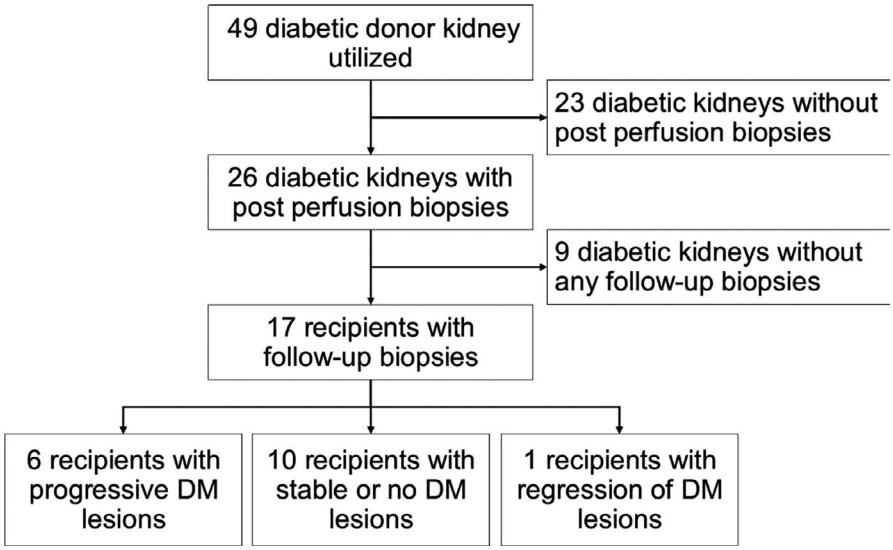


FIGURE 2 (STROBE diagram of histologic sampling cohort). Abbreviation: DM, diabetes

and interstitial fibrosis with tubular atrophy were noted in a significant number of post-perfusion biopsies with 57% of the donors with a diabetic history in this study also being hypertensive.

The findings from this study have implications for the KDPI. Despite varying duration of diabetic history, histological evidence of diabetic nephropathy was not seen in a majority of the post-perfusion biopsies, and where seen was mild. The evolution of diabetic nephropathy often requires long duration of diabetes with studies indicating that diabetic nephropathy occurs in only 30%-40% of type I and type II diabetics. However, it is a history of diabetes rather than the presence of diabetic nephropathy (as evidenced by proteinuria or impaired renal function) that is heavily weighted in the KDPI scoring. Given the histological findings in this study, the high numeric value given by KDPI to a diagnosis of diabetes results in a "labeling effect" and underutilization of otherwise acceptable kidneys.[16] Consistent with this "labelling effect," diabetes was reported in 5.6% of all deceased donor kidneys reported by Sung et al, however, a history of donor diabetes accounted for 39.5% of all the discarded kidneys.[17]

This study is limited by both the small sample size and the limited number of post-perfusion and follow-up biopsies. Though only 26 immediate post-perfusion biopsies were done in the donors with a diabetic history, this represented 53% of all such kidneys; substantially better than the SRTR/OPTN reported post-perfusion biopsy rate of 30%. In addition, although neither the post-perfusion nor follow-up biopsies were per protocol, but rather per transplant surgeon assessment in the former instance and per indication in the latter, this confounding should have favored the discovery of more rather than less pathologic change.

The strengths of this study include that, though small, this is the largest reported cohort of transplanted kidneys from donors with a diabetic history with post-perfusion biopsies, follow-up biopsies (in 50% of these), and correlation with clinical outcome. All prior analyses have had no biopsy correlation with outcomes[18] or are extensive clinical data analyses from the OPTN/SRTR database absent biopsy data.

In conclusion, although further studies are needed, the risk associated with transplantation of a kidney from a deceased donor with a diabetic history appears to be largely dependent on the diabetes

TABLE 4 Diabetic changes in 26 post-reperfusion biopsies of transplanted kidneys

RPS class[a]	Findings	Number of biopsies	Duration of diabetes in donors (number of donors)
0	No LM or EM changes	20	Unknown (7), #5 y (8), 6-10 y (3), >10 y (4)
I	No LM changes, but GBM thickening by EM	1	6-10 y (1)
IIa	Mild mesangial changes by LM	5	1-5 y (1) 6-10 y (3)[a]
IIb	Marked mesangial changes by LM	0	Not applicable
III	Mesangial nodules	0	Not applicable
IV	Sclerotic glomeruli	0	Not applicable

Abbreviations: EM, Electron microscopy; GBM, glomerular basement membrane; LM, light microscopy; RPS, renal pathology society.

[a]Two kidneys from the same donor.

status of the recipient. Furthermore, diabetic renal changes in conventionally accepted kidneys from donors with a diabetic history in this cohort are mild to minimal. This study suggests that the current emphasis of the KDPI on a donor diagnosis of diabetes should be revised to reflect the presence of high-grade proteinuria and renal function impairment. With such a change, it would be anticipated that fewer kidneys from donors with a diabetic history would be discarded than is currently the case. Finally, given the low 5-year patient survival in diabetic recipients of kidneys from donors with a diabetic history the propriety of transplanting such kidneys into diabetic recipients should be questioned.

ACKNOWLEDGEMENTS

This work was done by Dr Faiza Khan during her transplant nephrology fellowship at the Houston Methodist Hospital, Houston, TX.

CONFLICT OF INTEREST

None.

ORCID

Faiza N. Khan https://orcid.org/0000-0002-6093-5460

REFERENCES

1. Ojo AO, Hanson JA, Meier-Kriesche H, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol*. 2001;12(3):589-597.
2. Schold J, Meier-Kriesche H. Which renal transplant candidates should accept marginal kidneys in exchange for a shorter waiting time on dialysis? *Clin J Am Soc Nephrol*. 2006;1(3):532-538.
3. Ahmad M, Cole E, Cardella C, et al. Impact of deceased donor diabetes mellitus on kidney transplant outcomes: a propensity score-matched study. *Transplantation*. 2009;88(2):251-260.
4. Mohan S, Tanriover B, Ali N, et al. Availability, utilization and outcomes of deceased diabetic donor kidneys; analysis based on the UNOS registry. *Am J Transplant*. 2012;12(8):2098-2105.
5. Cohen J, Bloom R, Reese P, Porrett P, Forde K, Sawinski D. National outcomes of kidney transplantation from deceased diabetic donors. *Kidney Int*. 2016;89(3):636-647.
6. Abouna G, Kremer G, Daddah S, Al-Adnani M, Kumar S, Kusma G. Reversal of diabetic nephropathy in human cadaveric kidneys after transplantation into non -diabetic recipients. *Lancet*. 1983;322(8362):1274-1276.
7. American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care*. 2015;38(suppl 1):S8-S16.
8. Levey A, Stevens L. Estimating GFR using the CKD epidemiology collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis*. 2010;55(4):622-627.
9. Raftery A, Hoeting J, Volinsky C, Painter I, Yeung KY. BMA: Bayesian model averaging. R package version 3.18.4. http://CRAN.R-project.org/package=BMA
10. Dunson DB, Herring AH. Bayesian model selection and averaging in additive and proportional hazards models. *Lifetime Data Anal*. 2005;11(2):213-232.
11. Sumida K, Yamagata K, Iseki K, Tsubakihara Y. Different impact of hemodialysis vintage on cause-specific mortality in long-term hemodialysis patients. *Nephrol Dial Transplant*. 2016;31(2):298-305.
12. Sellarés J, de Freitas D, Mengel M, et al. Understanding the causes of kidney transplant failure: The dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*. 2011;12(2):388-399.
13. Bhalla V, Nast C, Stollenwerk N, et al. Recurrent and de novo diabetic nephropathy in renal allografts. *Transplantation*. 2003;75(1):66-71.
14. Schachtner T, Stein M, Reinke P. Diabetic kidney transplant recipients: Impaired infection control and increased alloreactivity. *Clin Transplant*. 2017;31(7):e12986.
15. Rao P, Schaubel D, Guidinger M, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation*. 2009;88(2):231-236.
16. Bae S, Massie A, Luo X, Anjum S, Desai N, Segev D. Changes in discard rate after the introduction of the kidney donor profile index (KDPI). *Am J Transplant*. 2016;16(7):2202-2207.
17. Sung R, Christensen L, Leichtman A, et al. Determinants of discard of expanded criteria donor kidneys: impact of biopsy and machine perfusion. *Am J Transplant*. 2008;8(4):783-792.
18. Comai G, Malvi D, Angeletti A, et al. Histological evidence of diabetic kidney disease precede clinical diagnosis. *Am J Nephrol*. 2019;50(1):29-36.

How to cite this article: Khan FN, Truong LD, Nguyen DT, et al. Outcomes of kidney transplantation using deceased donors with history of diabetes. *Clin Transplant*. 2020;34:e13775. https://doi.org/10.1111/ctr.13775