Donor Biopsy and Kidney Transplant Outcomes: An Analysis Using the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) Database

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Background. Although the degree of glomerulosclerosis on pretransplant donor biopsy is one criterion used in the decision to accept a deceased donor kidney, its relationship with graft survival remains controversial. This study compared graft survival with the degree of glomerulosclerosis found on donor biopsy. We also examined the agreement in degree of glomerulosclerosis between paired kidneys.

Methods. Biopsy results from 12,129 adult deceased donor transplants between January 1, 2000 and December 31, 2005 were identified in the Organ Procurement and Transplantation Network/United Network for Organ Sharing data, as of September 11, 2006. Of these, 2696 donors had both kidneys biopsied and subsequently transplanted.

Results. Among the groups with greater than 5% glomerulosclerosis, there was no statistically significant difference in graft survival rates (log-rank, $P=0.44$). The overall graft survival rates of the 0–5% group were significantly superior to those of the >5% groups (1-, 3-, and 5-year rates: 85.9%, 72.4%, and 59.0% for 0–5% group vs. 81.6%, 68.1%, and 53.6% for >5% group, log-rank $P<0.001$). Agreement between paired kidneys from the same donor was highest for the 0–5% glomerulosclerosis groups (90.6% for pairs with 0–5% glomerulosclerosis in the left kidney vs. 42.5% for pairs with >5% glomerulosclerosis in the left kidney).

Conclusion. Donor kidneys with less than 6% glomerulosclerosis were associated with better graft outcomes and intrapair agreement in the degree of glomerulosclerosis. Among kidneys with greater than 5% glomerulosclerosis, the degree of glomerulosclerosis did not help predict graft outcomes. Sampling error may contribute to the lack of outcome differences seen among these kidneys, given the low intrapair agreement.

Keywords: Donor biopsy, Kidney biopsy, Graft outcome, Kidney transplant, Glomerulosclerosis, Sampling error.

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Due to the growing disparity between supply and demand for deceased donor kidneys, there is an increasing interest in the use of kidneys from extended criteria donors (ECD) and other marginal donors, particularly for older recipients. ECD donors are defined as donors greater than 60 years of age or greater than 50 years of age with any two of the following criteria: a) hypertension; b) cerebrovascular accident as a cause of death; or c) donor terminal serum creatinine >1.5 mg/day (133 μmol/L; Table 1) (*1*). Kidneys from ECD donors are associated with a relative risk of graft failure of 1.7 or greater at 2 years posttransplant, compared with standard criteria donors (SCD).

Despite the increasing use of donor biopsies to risk-stratify marginal donors, histopathologic results are not incorporated into the definition ECD kidneys (*2–4*). In part, this reflects uncertainty regarding the prognostic utility of biopsy findings in predicting graft failure. Although an increasing body of evidence supports a role for vascular changes and interstitial fibrosis on donor biopsy in predicting graft outcomes, the use of glomerulosclerosis remains controversial and its role is unclear (*5–9*). This is largely due to conflicting evidence regarding the accuracy of the degree of glomerulosclerosis in differentiating donor kidneys with a greater risk of inferior outcomes (*2*, *4*, *6*, *8–16*). Part of the rationale for the consideration of glomerulosclerosis on donor biopsy is the presumed relationship with nephron mass. The simplicity of its quantification (number of affected glomeruli/total number of glomeruli), in comparison to vascular and other histological findings, may also contribute to its use. While glomerulosclerosis is known to increase with age, variability in the prevalence of glomerulosclerosis is seen in biopsies from older donors (*8*, *17*). In addition, the degree of glomerulosclerosis in donors with diabetes and hypertension is likely to vary

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TABLE 1. Definition of extended criteria donor (*1*)

Donor condition	Donor age categories	
	50–59 years	≥60 years
CVA+HTN+creatinine >1.5 mg/dL	X	X
CVA+HTN	X	X
CVA+creatinine >1.5 mg/dL	X	X
HTN+creatinine >1.5 mg/dL	X	X
CVA		X
HTN		X
Creatinine >1.5 mg/dL		X
None of the above		X

CVA, cerebrovascular accident was the cause of death; HTN, history of hypertension at any time.

with duration and severity of disease, as well as genetic factors. In this study we performed a large-scale retrospective analysis of the relationship between percent glomerulosclerosis and graft outcomes, using the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) database. We also examined the agreement in percent glomerulosclerosis among kidney pairs.

MATERIALS AND METHODS

Study Design

Biopsy results from 12,129 adult (aged >20 years) deceased donor transplants between January 1, 2000 and December 31, 2005 were identified in the OPTN/UNOS data, as of September 11, 2006. Multiorgan and dual kidney transplants were excluded from analysis. Percent glomerulosclero-

TABLE 2. Characteristics of donors, recipients, and grafts according to percent glomerulosclerosis

	Glomerulosclerosis					
	0–5%	6–10%	11–15%	16–20%	>20%	*P* value
N	8,767	1,792	669	349	552	
Donor						
Age (years)	50.7±11.3	54.4±10.0	55.9±9.5	54.3±11.0	53.1±9.8	<0.001
Creatinine (mg/dL)	1.2±1.0	1.1±0.7	1.2±1.3	1.2±0.8	1.3±1.4	<0.001
Blood urea nitrogen (mg/dl)	16.1±10.1	16.4±10.4	16.7±10.0	16.5±12.2	15.9±8.6	0.57
Female (%)	44.4	51.8	51.3	52.7	47.6	<0.001
Black (%)	12.2	11.9	10.8	13.5	11.2	0.69
Extended criteria donor (%)	39.6	51.9	59.7	57.0	46.9	<0.001
Cause of death (%)						<0.001
Anoxia	11.7	12.0	9.0	10.9	13.0	
Cerebrovascular accident	64.6	70.5	75.8	71.6	67.4	
Trauma	21.6	15.2	14.5	15.8	17.9	
Others	2.1	2.3	0.7	1.7	1.6	
Donor after cardiac death (%)	7.7	5.5	3.9	6.6	4.2	<0.001
HCV antibody positive (%)	3.6	1.8	1.8	2.9	2.4	<0.001
HBV core antibody positive (%)	6.6	7.4	7.3	6.6	7.3	0.77
Urinary tract infection (%)	8.5	8.3	9.3	10.3	16.9	<0.001
Clinical infection (%)	26.7	25.6	26.6	24.4	35.3	0.001
Diabetes (%)	10.3	13.6	12.9	14.0	13.4	<0.001
History of hypertension (%)	45.7	53.4	55.0	54.7	56.3	<0.001
History of smoking (%)	46.2	46.5	45.3	46.7	56.2	0.001
Recipient history						
Age (year)	52.8±12.4	53.9±12.4	55.2±12.1	56.3±11.4	54.4±12.4	<0.001
Peak panel reactive antibody (%)	14.1±26.8	13.9±26.2	11.3±23.3	11.7±24.7	14.3±26.8	0.10
Waiting (day)	773±647	838±699	782±622	782±661	870±681	<0.001
Female (%)	38.7	38.0	40.1	41.0	42.2	0.36
Black (%)	31.4	31.0	30.6	28.9	29.7	0.80
Regraft (%)	10.2	11.9	9.0	5.7	9.6	0.005
Medicare (%)	28.5	29.6	30.3	27.2	25.4	0.29
Diabetes (%)	32.9	34.9	35.1	35.0	34.1	0.38
HCV antibody positive (%)	6.4	6.3	5.2	4.6	4.4	0.15
Transplant						
Cold ischemia time (hr)	19.5±8.3	20.6±8.6	20.5±8.8	22.1±9.5	20.4±9.2	<0.001
Number of human leukocyte antigen A/B/DR mismatches	3.8±1.7	3.9±1.7	3.9±1.7	3.8±1.7	3.9±1.6	0.23

TABLE 3. Univariate and multivariate cox regression analyses

Factors	Unadjusted		Adjusted	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Donor				
Age				
21–40 years	1.0		1.0	
41–50 years	1.27 (1.12–1.45)	<0.001	1.20 (1.05–1.37)	0.006
>50 years	1.60 (1.43–1.80)	<0.001	1.32 (1.16–1.52)	<0.001
ECD vs. SCD	1.42 (1.32–1.52)	<0.001	1.22 (1.11–1.34)	<0.001
Female vs. male	1.14 (1.06–1.22)	<0.001	1.10 (1.03–1.18)	0.007
HCV antibody (+ vs. –)	1.41 (1.18–1.69)	<0.001	1.18 (0.96–1.46)	0.12
HBV core antibody (+ vs. –)	1.16 (1.02–1.33)	0.02	1.09 (0.96–1.25)	0.19
Black vs. others	1.23 (1.11–1.36)	<0.001	1.21 (1.09–1.35)	0.001
Diabetes vs. others	1.33 (1.20–1.48)	<0.001	1.30 (1.17–1.44)	<0.001
Recipient				
Age >60 vs. ≤60 years	1.42 (1.32–1.53)	<0.001	1.38 (1.27–1.49)	<0.001
Male vs. female	1.14 (1.06–1.23)	<0.001	1.17 (1.08–1.26)	<0.001
Black vs. others	1.33 (1.24–1.43)	<0.001	1.27 (1.18–1.37)	<0.001
HCV antibody (+ vs. –)	1.39 (1.22–1.58)	<0.001	1.28 (1.10–1.49)	0.001
Medicare vs. others	0.75 (0.69–0.82)	<0.001	0.81 (0.75–0.88)	<0.001
Regraft vs. primary	1.26 (1.13–1.40)	<0.001	1.36 (1.21–1.53)	<0.001
PRA >50 vs. 0–50%	1.26 (1.13–1.40)	<0.001	1.33 (1.18–1.49)	<0.001
Diabetes vs. others	1.28 (1.19–1.38)	<0.001	1.22 (1.14–1.32)	<0.001
No. of HLA A, B, DR antigen mismatches				
0	1.0		1.0	
1–4	1.19 (1.04–1.35)	0.01	1.13 (0.99–1.29)	0.07
5–6	1.36 (1.19–1.55)	<0.001	1.23 (1.07–1.41)	0.003
Glomerulosclerosis >5% vs. 0–5%	1.23 (1.14–1.33)	<0.001	1.15 (1.06–1.24)	<0.001

CI, confidence interval; RR, relative risk; ECD, extended criteria donor; SCD, standard criteria donor; HCV, hepatitis C virus; HBV, hepatitis B virus; PRA, panel reactive antibody.

sis was as reported by the organ procurement organization (OPO). Indication for biopsy and biopsy technique were not reported. Vascular and interstitial histopathologic findings were also not reported. The cohort was divided into five groups according to degree of glomerulosclerosis on biopsy with Group 1 having 0 to 5%, Group 2 with 6 to 10%, Group 3 with 11 to 15%, Group 4 with 16 to 20% and Group 5 with greater than 20% glomerulosclerosis. Biopsies with greater than 20% glomerulosclerosis were included in one group to preserve statistical power, due to small sample size. Outcomes included: graft survival; incidence of delayed graft function (DGF), defined as the need for dialysis within the first week after transplantation; incidence of immediate graft function (IGF) defined as a decline in serum creatinine of at least 25% within the first 24 hr after transplantation; cumulative incidence of acute rejection (AR); and serum creatinine concentration. We also examined the agreement in donor percent glomerulosclerosis between paired kidneys that were both biopsied and subsequently transplanted (2696 pairs).

Statistical Methods

Kaplan-Meier product limit method was used to assess graft survival rates. Patient death was considered as graft loss. Chi-square test was used for categorical variables and Kruskal-Wallis rank sum test for continuous variables (Table 3). Univariate Cox regression analysis was used to examine the relationship between various donor and recipient factors and outcomes. Multivariate Cox regression analysis was used to determine the effect of percent glomerulosclerosis on graft failure, after controlling for other determinants of graft function, based on the results of univariate analysis. In order to measure interrater agreement between left and right kidney biopsies from the same donor, Cohen's kappa coefficient was estimated using STATA version 9 (Fig. 1).

RESULTS

The majority of biopsies contained 0–5% glomerulosclerosis (n=8767, 72.3%), followed by biopsies with 6–10% glomerulosclerosis (n=1792, 14.8%; Table 2). Female sex, ECD status, a history of hypertension, and a history of diabetes mellitus were less common in the 0–5% group compared to the >5% groups. This group was also associated with younger mean age. Donation after cardiac death (DCD) status and hepatitis C virus antibody positivity were more common in this group. Urinary tract infection, clinical infection, and smoking were more common in the >20% GS group compared to all other groups. While there was a statistically significant difference in mean values of terminal serum creatinine, recipient age, waiting time, and cold ischemia time

among the glomerulosclerosis groups, the clinical differences were small. There were no significant differences in the degree of human leukocyte antigen matching or recipient Medicare status.

Graft Survival

Among the groups with greater than 5% glomerulosclerosis, there was no statistically significant difference in graft survival rates (Fig. 3, log-rank, $P=0.44$). The overall graft survival rates of the 0–5% group were significantly superior to those of the >5% groups (1-, 3-, and 5-year rates: 85.9%, 72.4%, and 59.0% for 0–5% group vs. 81.6%, 68.1%, and 53.6% for >5% group, log-rank $P<0.001$; Fig. 2).

Other Outcomes

There were no significant differences in the incidence of IGF, DGF, and AR (data not shown). However, a greater proportion of the 0–5% group had a serum creatinine concentration of 0.1–1.5 mg/dL, compared to the other four groups (44.7% vs. 36.8, 28.2, 39.6, and 41.6% for 6–10%, 11–15%, 16–20%, and >20% groups respectively, $P<0.001$).

Cox Regression Analysis

Statistically significant risk factors in univariate analyses were included in multivariate analysis (Table 3). After adjustment for 16 potential risk factors, >5% glomerulosclerosis was associated with a higher risk of graft failure compared to 0–5% glomerulosclerosis (RR=1.15, $P=0.001$).

Paired Kidney Analysis

When comparing percent glomerulosclerosis of the left and right kidney from the same donor, the agreement was 78.5% (Cohen's kappa=0.51 with standard error=0.009, $P<0.001$ vs. null hypothesis of kappa=0; Fig. 1). Using the left kidney as the reference group, the proportion of paired kidneys falling into the same glomerulosclerosis category was 90.6% for the 0–5% group, 50.8% for the 6–10% group; 31.1% for the 11–15%; 24.8% for the 16–20%; and 63.4% for the >20% group. Results were similar when using the right kidney as the reference group (90.2%, 49.8%, 30.2%, 27.9%, and 70.0%, respectively). Agreement decreased with increasing glomerulosclerosis, with the exception of the >20% GS group.

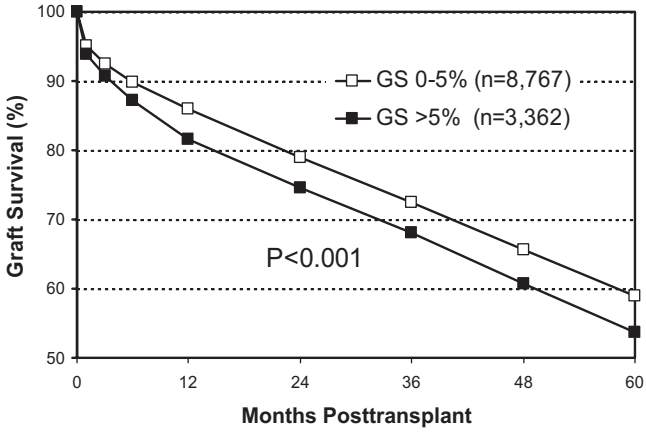

FIGURE 2. Overall graft survival.

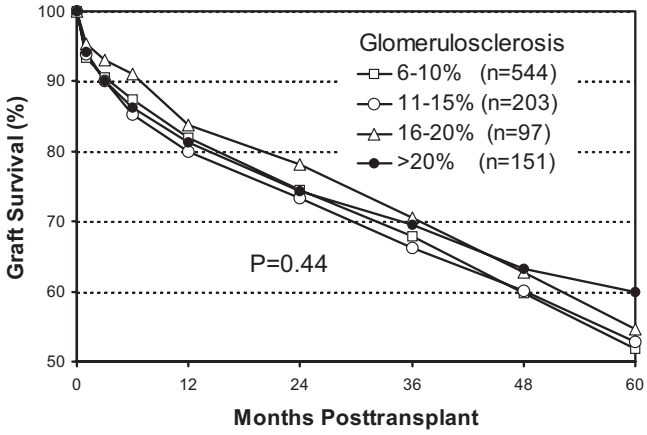

FIGURE 3. Overall graft survival (glomerulosclerosis<5%).

DISCUSSION

This study uses the largest database of kidney transplants in the United States to evaluate the relationship

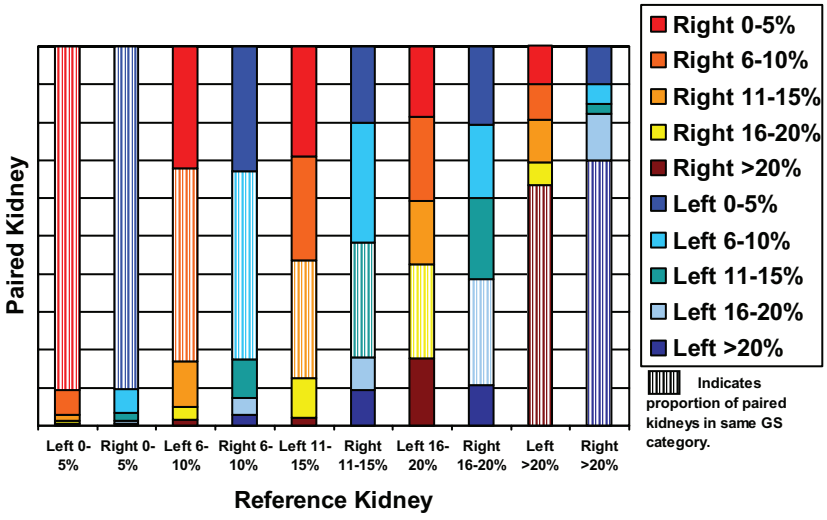

FIGURE 1. Percent glomerulosclerosis (GS) in paired kidneys. Overall Agreement=78.5%, expected agreement=55.8%, Cohen's Kappa=0.51 ($P<0.001$ vs. null hypothesis of Kappa=0).

between the degree of donor glomerulosclerosis and graft outcomes. We found that donor kidneys with greater than 5% glomerulosclerosis were associated with worse transplant outcomes, including decreased graft function at 1 year, and increased graft loss up to 4 years posttransplant. Among the cohort of kidneys containing >5% glomerulosclerosis, the degree of glomerulosclerosis was not associated with graft failure. Whereas kidney pairs containing at least one biopsy with 0–5% glomerulosclerosis had 90.2–90.6% intra-pair agreement, and those with >20% glomerulosclerosis had 63–70% agreement, kidneys with glomerulosclerosis in the 6–19% range showed little intrapair agreement.

There are a number of possible reasons for the absence of differences in outcomes seen in the >5% groups. One reason relates to the precision of the donor biopsy technique, which is largely dependent on biopsy size. For a randomly distributed focal glomerular process, such as glomerulosclerosis, the probability of having a given number of abnormal glomeruli follows a binomial distribution (*18–20*). Thus the percentage of abnormal glomeruli found on biopsy depends not only on the prevalence of pathology in the kidney but also on the total number of glomeruli present. Based on this assumption, it has been proposed that to detect a small (10%) difference in the percent of glomeruli affected, a minimum of 100 glomeruli would be needed (*18*). In their study of donor biopsy and graft outcomes, Wang et al. found that a baseline biopsy containing at least 25 glomeruli was needed to result in a statistically significant relationship between the degree of glomerulosclerosis and graft survival (relative risk: 1.056, confidence interval: 1.010–1.105, $P=0.017$) (*16*). When all biopsies were included, no association was found. This group also analyzed the agreement in degree of glomerulosclerosis between paired baseline biopsies and between baseline and follow-up biopsies. When comparing baseline to follow-up biopsies, they found that reproducibility of glomerulosclerosis increased with number of glomeruli. When the number of glomeruli reached 14, however, statistical significance was again lost, due to the small number of biopsies with greater than 14 glomeruli. When comparing the degree of glomerulosclerosis in baseline paired biopsies, which were done by wedge technique and contained a greater number of glomeruli, precision increased with biopsy size and became statistically significant only when >14 glomeruli were included ($r=0.83$, $P<.001$). After the exclusion of a single outlier, however, correlation decreased significantly. The lack of correlation between paired donor biopsies with respect to glomerulosclerosis has also been reported by others (*2*).

We also found a low degree of precision (i.e., agreement between paired kidneys) among kidneys with >5% glomerulosclerosis, particularly among the 6–19% groups. Because biopsy size is not reported in the UNOS/OPTN database, we were unable to include it in our analysis. Mean donor biopsy size as reported in the literature, though variable, is generally in the range of 10–35 glomeruli (*10*, *16*, *21–23*). Sampling error, therefore, is likely to play a significant role in the interpretation of donor biopsies with regards to the degree of glomerulosclerosis. The greater intrapair agreement in the 0–5% and >20% groups is predicted by the assumption of a binomial distribution as discussed above. Based on this model, the finding of either a very low or a very high degree of glomerulosclerosis would be a more reliable indicator of the extent of disease than the finding of an intermediate degree of glomerulosclerosis. The lack of precision in the 6–19% range would explain the absence of a graded decline in graft function with increasing degrees of glomerulosclerosis.

Sampling error/inadequate biopsy size may explain the conflicting results seen in prior studies. In addition, prior analyses were largely limited to a threshold value of 20%. An early study by Gaber et al. suggested that donor glomerulosclerosis greater than 20% increased the risk of DGF, impaired graft function at 6 months, and graft loss (*11*). In their retrospective analysis of 65 baseline biopsies of kidney allografts, DGF occurred in 22%, 33%, and 87% of recipients with no glomerulosclerosis, <20% glomerulosclerosis, and >20% glomerulosclerosis, respectively ($P<0.05$). Furthermore, at 1-year follow-up, graft loss occurred in 7% of recipients of kidneys with less than 20% glomerulosclerosis compared to 38% in recipients with greater than 20% glomerulosclerosis ($P<0.04$). In contrast to the results reported by Gaber et al., subsequent studies by independent investigators failed to demonstrate a correlation between >20% glomerulosclerosis and DGF or graft survival. A correlation between >20% glomerulosclerosis and graft function, however, has been reported. In a retrospective review of 89 recipients of deceased donor kidneys that were biopsied at implantation, Lu et al. found that recipients with ≥20% glomerulosclerosis had a higher serum creatinine at 1 and 2 years, but similar rates of DGF and 2-year graft survival despite older age and increased incidence of hypertension in this group (*12*). Similarly, in a European prospective study consisting of 200 consecutive deceased donors, Pokorna et al. found no significant differences in the incidence of DGF or graft survival rates among kidney donors with 0–19% vs. >20% GS, after donor age was accounted for (*4*, *13*). Graft function at 3 weeks and at 1 year, as determined by creatinine clearance, however, was significantly reduced in patients receiving a kidney with ≥20% glomerulosclerosis. In an analysis of the UNOS/OPTN database, Edwards et al. also used a 20% cutoff in their analysis of donor glomerulosclerosis and graft outcomes (*2*). They found that calculated donor creatinine clearance correlated with 1-year graft survival and function, whereas no significant correlation was found between the percentage of glomerulosclerosis and either outcome.

With the exception of the study by Gaber's group, the above studies, like ours, failed to show increased risk of DGF or graft failure with >20% glomerulosclerosis. The limitation of analysis to a 20% threshold, however, would have failed to detect an association between lesser degrees of glomerulosclerosis and graft survival, even if such an association existed. The study by Gaber et al. was characterized by small sample size and a particularly high degree of glomerulosclerosis. Multivariate analysis was not included, making it difficult to separate the effects of age and other risk factors from those of glomerulosclerosis. In addition, biopsy size in these studies was either not reported (*2*); reported only as >10 glomeruli, (*11*, *12*) or in the case of the Pokorna study, reported as 27.6 ± 16 glomeruli with a range of 6–101 (*13*). With relatively small study popula-

tions, biopsies containing even as many as 30 glomeruli, on average, would be unlikely to show statistically significant differences in outcomes.

Sampling error may also be introduced by the preferential distribution of glomerulosclerosis in the subcapsular cortex. Maruve et al. compared donor wedge biopsies from discarded kidneys from donors greater than age 54 with autopsy sections taken throughout the kidney (*24*). They found that wedge biopsies, which result in a more superficial sample than core biopsies, overestimated the true degree of glomerulosclerosis. They also found that glomerulosclerosis was variable in severity throughout the rest of the kidney. Because biopsy technique is not reported in the UNOS/OPTN database, we were unable to analyze its impact, if any, on our findings.

Besides sampling error, the lack of differences in outcomes among the >5% groups could be due to a true absence of a relationship between glomerulosclerosis on biopsy and graft outcomes in these kidneys. Our study cannot address this possibility due to its retrospective nature and the associated selection bias.

Our inability to demonstrate a statistically significant increase in graft failure in the 16–20% and >20% groups compared to the 0–5% group could similarly be due to decreased reliability of biopsy findings and/or a true absence of such a relationship. Alternatively, this finding may be due to insufficient statistical power. Out of 12,129 biopsies, only 901 (7%) contained >16% glomerulosclerosis. Because the confidence interval crossed one, it is also possible that these kidneys were associated with improved graft survival.

Although we show that kidneys with >5% glomerulosclerosis were at higher risk for graft failure, the results of this study cannot be used to determine which kidneys should be discarded. Because kidney biopsy results are only one criterion used by transplant centers, kidneys with significant glomerulosclerosis that are accepted for transplantation are likely to have better clinical features than discarded kidneys. They are therefore not necessarily representative of all potential deceased donor kidneys. Given a relative survival difference of 4%, however, our results do demonstrate acceptable outcomes in well-selected kidneys with >5% glomerulosclerosis on biopsy. The adjusted relative risk of failure of a graft with >5% glomerulosclerosis on biopsy is just slightly greater than that of a graft from a female donor, and less than that of a graft from either a black donor or a donor aged 41–50. Inadequate statistical power limits our ability to draw conclusions on the use of kidneys with higher degrees (>16%) of glomerulosclerosis.

Randhawa et al. examined the relationship between donor glomerulosclerosis and outcomes in ECD transplants (*8*). They found a relationship between increasing glomerulosclerosis up to 30%, and graft function, though graft failure was not specifically examined. This subgroup was not analyzed in the current study. Prior studies have also evaluated the relationship between graft outcomes and vascular and interstitial changes, with conflicting results (*5–9*). These findings could not be included in the current study for the reasons already discussed. In addition, outcomes were limited to short-term follow-up.

CONCLUSION

The findings of this study showed that glomerulosclerosis >5% on renal biopsy was a useful predictor for worse graft outcomes. The magnitude of the difference in graft survival between kidneys with 0–5% glomerulosclerosis and >5% glomerulosclerosis was approximately 4–5% from 1 to 4 years posttransplant. They also showed that with glomerulosclerosis >5%, the percentage of glomerulosclerosis did not add prognostic information about graft survival. This may be partly explained by the poor precision of biopsy results in predicting the degree of glomerulosclerosis, as evidenced by the poor intrapair agreement. Limitations in biopsy size may continue to limit the usefulness of estimates of the degree of glomerulosclerosis in predicting graft outcomes. Future large-scale studies incorporating other histological parameters of kidney damage as well as the impact of biopsy technique may help further define the utility of donor biopsy. To this end, we recommend including fibrotic and vascular changes in the UNOS database.

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