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Correlation of histologic findings on preimplant biopsy with kidney graft survival

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Summary

Kidney biopsies are being used to evaluate marginal deceased donor organs, but, the literature on the utility of this practice remains conflicting. We re-examined this issue by performing a multivariate analysis of 597 kidney transplant recipients. The presence of moderate arteriosclerosis and/or moderate arteriolosclerosis (MA), defined as ≥25% luminal compromise, was a significant predictor of graft outcome in standard criteria donors (multivariate, $P = 0.01$) and in expanded criteria donors (ECD) as defined by UNOS criteria (univariate $P = 0.02$). One-, 3-, and 5-year overall allograft survival with MA was 71%, 58%, and 40%, respectively. Increasing degrees of glomerulosclerosis (GS) were associated with earlier graft failure on univariate ($P = 0.03$) but not multivariate analysis ($P = 0.36$). GS > 20% and interstitial fibrosis >25% had a low frequency in the material reviewed, likely reflecting our organ utilization practices, and did not have a demonstrable effect on graft outcome. Clinical parameters independently associated with worse graft function were ECD status ($P < 0.05$), retransplantation ($P = 0.004$), recipient age ($P < 0.05$), and delayed graft function ($P < 0.0001$). Donor vascular disease is an independent risk factor for suboptimal graft survival. Great caution should be exercised in the decision to transplant kidneys with moderate arterial and/or arteriolar luminal narrowing.

Introduction

Because of the disparity between organ supply and demand, kidneys from marginal donors, such as expanded criteria donors (ECD), older donors, or donors with evidence of chronic lesions, are being transplanted with increasing frequency [1,2]. However, there is evidence that kidney recipient outcome from these higher risk, primarily older donors is worse; delayed graft function (DGF) rates are higher, and short- and long-term graft survival outcomes are worse than with ideal kidney allografts [2–6]. Recent evidence suggests that if older donor kidneys are allocated based on a preimplantation histologic assessment, kidneys from donors >60 years of age survive as long as transplants from younger donors (although such allocation is also associated with high rates of dual transplantation) [7]. In a multivariate analysis, Remuzzi *et al.* [7] showed that the risk of graft failure in patients aged >60 years was 3.68 times greater when transplanted kidneys were not histologically assessed. Logarithmic projections of 10-year outcomes in recipients of kidneys from donors aged >60 years indicated that death or graft failure would occur in 9/100 patients whose transplants underwent preimplantation biopsy, compared with 44/100 patients whose transplants did not undergo preimplantation biopsy [7]. A kidney biopsy can define the degree of pathologic deterioration present, and thereby help with the assessment of its suitability for transplantation.

Previous studies have analyzed pretransplantation predictors of post-transplantation outcomes [8–19]. Interstitial fibrosis, glomerulosclerosis (GS), arteriolar hyalinosis,

and/or arteriosclerosis have variably been identified as critical parameters in predicting DGF and/or poor function. However, many of these studies have methodological flaws such as small sample size, insufficient histological detail for critical evaluation, biopsies with only mild histological changes, and lack of correction for covariates.

In this paper, we reviewed our single-center experience with adult single kidney transplantation to determine pre- and post-transplant factors that, either alone or in combination, could predict post-transplant graft survival.

Materials and methods

Selection of patients

Between January 1987 and October 2006, 2784 single-kidney-only transplants were performed in adult patients at the University of Pittsburgh Medical Center. In 2029 of these patients, a pretransplant donor kidney biopsy was not performed. In the other 755 recipients, a donor kidney biopsy had been performed prior to transplantation. Of these 755 biopsies, 151 were excluded as they were from donors <30 years of age. Another five cases were excluded because of incomplete clinical information or follow-up data within the first post-transplantation year, and two were excluded because of the presence of >30% fibrin thrombi in the specimen. The remaining 597 patients were included; they were transplanted between 1989 and 2006; and all had at least 1 year of follow-up.

Histologic evaluation

The biopsy specimens evaluated were wedge biopsies with two to four hematoxylin–eosin-stained sections available for review. Periodic acid-Schiff and trichome stains were performed in all cases. On average, 66 glomeruli were obtained per sample (range 2–295). In 38 kidney biopsies, there were fewer than 10 glomeruli; however, the number of glomeruli obtained from the contralateral kidney of the same donor [available in 28 of the 38 cases (74%)] was more than 10. Histologic findings of the contralateral kidneys were similar and therefore considered representative. The majority (94%) of kidney biopsies contained at least one artery and one arteriole. In 33 kidney biopsies an artery ($n = 2$) and/or arteriole ($n = 31$) was not present; however, the contralateral kidney of the same donor contained the missing artery and/or arteriole in 100% and 71% of cases, respectively. The degree of GS was categorized into grades 0–4 corresponding to 0%, 1–9%, 10–19%, 20–29%, and ≥30% global sclerosis, respectively. The degree of interstitial fibrosis, arteriosclerosis, and arteriolosclerosis were graded as mild, moderate, or severe. The interstitial fibrosis score was mild when <25% of the sample showed interstitial fibrosis, moderate when 25–50% fibrosis was observed, and severe with >50% interstitial fibrosis present. The vascular score was mild, moderate, and severe when degree of luminal compromise was <25%, 25–50%, and >50%, respectively.

Clinical data

Patient and donor data were retrospectively compiled primarily from the medical center transplant database. Chart reviews were performed when specific information was not available from the database. Data analysis was approved by the University of Pittsburgh Institutional Review Board (# 0602112).

The primary end point of the study was 1-year graft survival. Secondary endpoints were overall patient and graft survival. Pretransplantation variables collected included demographic, histologic, and baseline characteristics, as shown in Tables 1 and 2. Post-transplant data obtained were limited to graft failure [defined as return

Table 1. Recipient demographic and transplant characteristics.

Characteristic	Result
Age, Mean (years ± SD)	54 ± 11
Male	59%
Race	
White	83%
African-American	16%
Other	1%
Previous kidney transplant	
0	86%
1	11%
2	2%
3	1%
Waiting time	
Mean (days ± SD)	423 ± 401
Median	319
Panel reactive antibodies ≥10%	12%
End-stage renal disease	
Glomerulonephritis	16%
Hypertension	21%
Diabetes	31%
Other	33%
Induction	
Campath	34%
Thymoglobulin	10%
None or IL2-R blocker	56%
Cold ischemia time	
Mean (hours ± SD)	25 ± 9
Median	25
HLA ABDR mismatch, Median	4
Delayed graft function	33%
Acute rejection 365-day post-transplantation	42%
Campath	23%
Thymoglobulin	66%
None or IL2-blocker	49%

Table 2. Donor demographic and biopsy characteristics.

Characteristic	Result
Deceased by cardiac death	6%
Cause of death, cerebrovascular accident	43%
Age	
Mean (years ± SD)	52 ± 10
Median, Range	52, 30–78
Male	45%
History of hypertension	42%
History of diabetes mellitus	10%
Terminal creatinine >1.5 mg/dl	14%
Expanded criteria donor	28%
Machine-perfused kidney	19%
Glomerulosclerosis (%)	
0	15%
1–9	62%
10–19	19%
20–29	3%
>30	1%
Interstitial fibrosis	
<25%	97%
25–50%	3%
>50%	0%
Arteriosclerosis	
<25%	92%
25–50%	7%
>50%	<1%
Arteriolosclerosis	
<25%	93%
25–50%	7%
>50%	<1%
Any vascular luminal narrowing ≥25%	11%

to hemodialysis, transplant nephrectomy, or death], DGF [hemodialysis within the first week post-transplantation], and biopsy-confirmed acute rejection within 365 days of transplantation.

The definition of ECD included all donors aged 60 years and older and those aged 50–59 years with at least two of three other conditions (cerebrovascular cause of death, terminal creatinine >1.5 mg/dl, and hypertension) [20]. Human leukocyte antigen (HLA) typing was performed by sequence specific priming using commercial SSP kits (One Lambda, Canoga Park, CA, USA: Pel Freez, Brown Deer, WI, USA). Machine perfusion was initiated by the local organ procurement organization and selectively became available in September 2005. Our selection criteria for kidney acceptance is generally a perfusion flow >0.9 ml/min/g and resistive index <0.4 mmHg/ml/min/g.

Immunosuppression and treatment of rejection

Tacrolimus (Prograf; Astellas Pharmaceuticals Inc., Deerfield, IL, USA) was used as the primary immunosuppressive agent. Only one patient, transplanted in 1989, received cyclosporine. Before 2001, induction therapy was generally not used, and most recipients received double or triple immunosuppression with steroids, azathioprine, mycophenolate mofetil, or sirolimus. Beginning in July 2001, the majority of patients were given an immunosuppressive regimen based upon pretreatment with polyclonal rabbit anti-human thymocyte globulin (Thymoglobulin; Genzyme Transplant, Cambridge, MA, USA) or alemtuzumab (Campath-1H; Berlex, Seattle, WA, USA), and followed by steroid-free post-transplant low dose tacrolimus monotherapy (target trough level of10 ng/ml) as previously described [21]. After March 2003, Thymoglobulin had been abandoned in favor of alemtuzemab. For the purposes of this analysis, the majority of patients (56%) did not receive antilymphocyte depletion medication as these therapies had been administered only within the last 5 years of the study.

Episodes of biopsy-proven rejection were treated with one or more of the following regimens: 1–1.5 g of intravenous methylprednisolone, Thymoglobulin 1 mg/kg/day for 5 days, 30 mg IV Campath-1H, alternate day plasmapheresis followed by IVIg 100 mg/kg, and/or high dose IVIg 2 g/kg. Maintenance immunosuppression was also amplified following the diagnosis of rejection in the majority of patients.

Statistical analysis

The calculated medians of continuous variables were used as the differentiating points. Some continuous variables were organized into clinically significant thresholds. These included recipient and donor age ≥60 years, and cold ischemia time >24 h. Several categorical variables required simplification to achieve statistically meaningful outcomes including causes of end-stage renal disease, race, panel-reactive antibody, and retransplantation.

Patient and graft survival were computed using Kaplan–Meier methods. Death with a functioning transplant was considered a graft loss. Proportions were compared using the chi-squared test. Univariate and multivariate analyses were conducted using the log-rank test. Variables that were significant at the $P < 0.10$ univariate level were included in multivariate analysis. A P-value <0.05 was considered significant. All analyses were performed using SAS software, version 8.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 597 adult kidney transplant recipients of histologically evaluated kidneys 83% were Caucasian, 16% were African American, and 1% were Indian-subcontinental or

Asian (Table 1). Fifty-nine percent of the recipients were male. The majority of the subjects were recipients of their first renal allograft (86%), followed by 11% undergoing their second, 2% their third, and 1% their fourth transplants. Panel-reactive antibody levels ≥10% prior to transplantation existed in 12%. Donors were on average 52 ± 10 years of age; 21% were ≥60 years of age, and 28% were ECDs (Table 2). The frequencies of GS ≥ 20%, interstitial fibrosis ≥ 25%, and/or any vascular (artery or arteriole) luminal narrowing ≥ 25% (MA) were 4%, 3%, and 11%, respectively. There were no cases with interstitial fibrosis >50%, there was one case of arteriosclerosis >50%, and two cases of arteriolosclerosis >50%. Post-transplantation, DGF occurred in 33%, and acute rejection within 365 days in 42% (Table 1).

The actuarial graft survival at 1, 3, 5, and 10 years after kidney transplantation was 84%, 67%, 49%, and 31% and patient survival was 94%, 83%, 67%, and 47%, respectively. Figure 1 depicts graft and patient survival stratified by the presence or absence of MA. Patient survival at 1, 3, and 5 years for recipients of kidneys with MA was 87%, 53%, and 45%; and significantly worse than those who received kidneys without MA ($P = 0.005$). Graft survival at 1, 3, and 5 years for recipients of kidneys with MA was 71%, 58%, and 40%. Compared to cases without MA, there was a trend toward worse outcomes ($P = 0.08$). The largest difference in graft survival between the two groups was seen in the first year, with smaller differences in subsequent years. As 34% of the recipients of kidneys with MA did not have follow-up beyond 1 year, univariate and multivariate analyses were performed to detect the impact of variables on 1-year allograft survival.

Table 3 depicts the results of the univariate and multivariate analysis. Both donor age ≥60 ($P = 0.008$) and ECD status ($P = 0.002$) were significant on univariate analysis; however, as these two variables are related and can overlap only ECD, the stronger predictor of the two, was included in the multivariate analysis. Significant independent clinical predictors of graft failure at 1 year were: ECD status ($P < 0.05$), retransplantation ($P = 0.004$), recipient age ≥60 years ($P < 0.05$), DGF ($P < 0.0001$), and MA ($P = 0.01$). Recipient hypertension demonstrated a protective effect compared to the other two categories of end-stage renal disease, diabetes and glomerulonephritis ($P = 0.04$).

Inclusion of donor age ≥60 years as a covariate, instead of ECD status, was also an independent predictor of poor early outcomes and did not change the significant findings of the other variables. Additionally, removal of the three cases with severe vascular narrowing, the 20 cases with insufficient glomeruli counts ($n = 10$) and/or arteriole density ($n = 9$) and no contralateral kidney for comparison did not change the results appreciably.

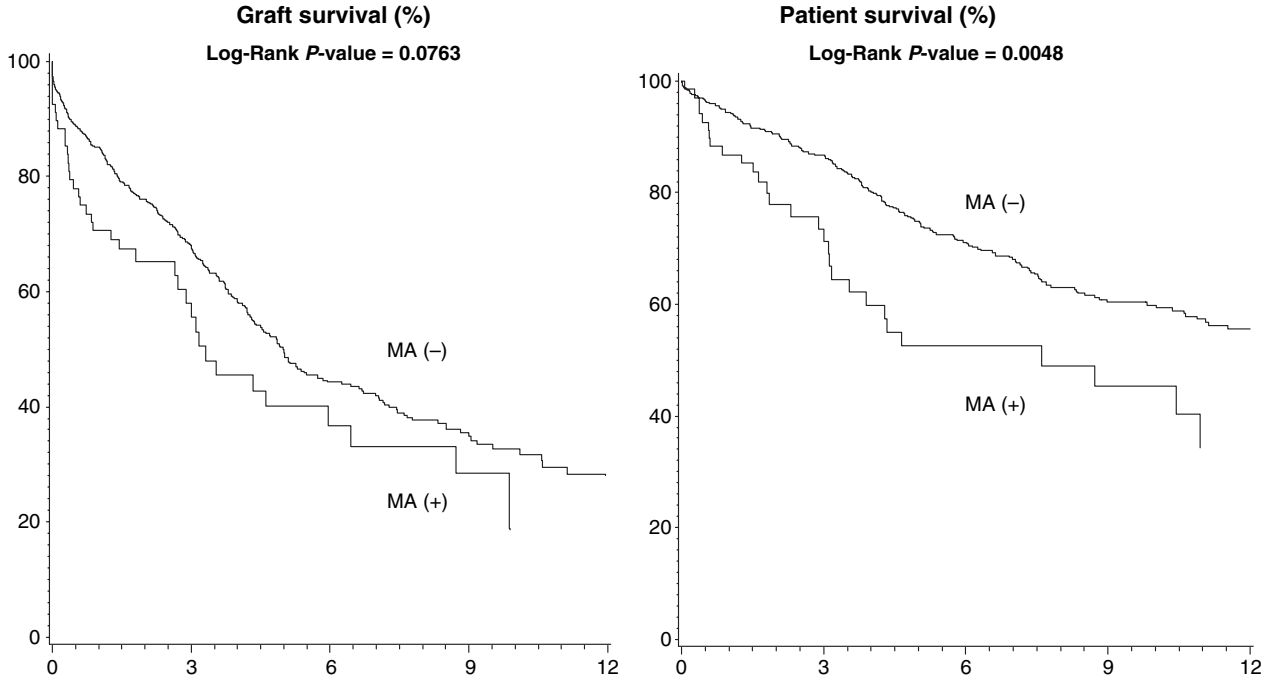

Figure 1 Graft and patient survival post-transplantation are shown as percent survival versus time in years. The influence of moderate arterio- or arteriolo-sclerosis (MA) is shown by separating grafts without MA [MA(–)] from grafts with ≥25% luminal narrowing [MA(+)].

Table 3. Univariate and multivariate analysis of risk factors for 1-year graft failure.

	Univariate*			Multivariate		
Group	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Recipient >60 years	1.65	1.07–2.56	0.0244	1.68	1.01–2.79	0.0452
Retransplantation	2.04	1.18–3.51	0.0102	2.42	1.32–4.44	0.0044
Hypertension	0.54	0.29–1.01	0.0524	0.50	0.26–0.95	0.0358
Long wait: >319 days	1.82	1.17–2.54	0.0081	1.52	0.95–2.45	0.0843
Expanded criteria donor	2.02	1.29–3.17	0.0022	1.70	1.01–2.86	0.0466
Delayed graft function	3.65	2.33–5.70	<0.0001	3.63	2.27–5.78	<0.0001
Vascular luminal narrowing ≥25%						
Arterial	2.23	1.13–4.43	0.0216			
Arteriolar	1.55	0.74–3.26	0.2435			
Either arterial or arteriolar	2.41	1.36–4.30	0.0027	2.30	1.21–4.36	0.0111
Glomerulosclerosis category	1.35	1.02–1.78	0.0349	1.16	0.85–1.58	0.3635

OR, odds ratio; CI, confidence interval; CVA, cerebrovascular accident.

*Donor age >60 years was significant on univariate analysis (OR 1.92, CI 1.19–3.10, $P = 0.0079$) but not included due to overlap with ECD status. The other variables tested did not meet criteria ($P < 0.10$) for inclusion into the multivariate analysis and include the following: female recipient ($P = 0.99$), African-American recipient ($P = 0.63$), end-stage renal disease due to toglomerulonephritis ($P = 0.67$), diabetes ($P = 0.85$), or other cause ($P = 0.24$), panel reactive antibody ≥10% ($P = 0.11$), female donor ($P = 0.34$), donor death due to cerebrovascular accident ($P = 0.61$), donor hypertension ($P = 0.16$), donor diabetes ($P = 0.89$), deceased after cardiac death ($P = 0.96$), donor terminal creatinine >1.5 mg/dl ($P = 0.84$), machine perfusion ($P = 0.87$), cold ischemia time >24 ($P = 0.54$), >36 ($P = 0.91$), or >48 h ($P = 0.83$), HLA-ABDR mismatch >3 ($P = 0.11$), Campath induction ($P = 0.72$), Thymoglobulin induction ($P = 0.58$), acute rejection within 365-day post-transplant ($P = 0.48$), and interstitial fibrosis 25–50% ($P = 0.54$).

Moderate arteriosclerosis (alone) was significantly associated with 1-year graft failure on univariate analysis (Table 3) and showed a trend toward significance on multivariate analysis (odds ratio 2.09, confidence interval 0.98–4.50, $P = 0.058$). Moderate arteriosclerosis correlated with the degree of GS ($P = 0.001$). The frequency of moderate arteriosclerosis in GS categories 0, 1, 2, 3, and 4 were 1% (1/90), 7% (25/371), 14% (16/111), 6% (1/18), and 29% (2/7).

Moderate arteriolosclerosis (in arterioles as opposed to arteriosclerosis in more proximal vessels) was not found to be a significant predictor of 1-year graft outcomes on univariate or multivariate analysis. MA correlated with degree of GS ($P = 0.04$) and was found in 0% (0/90), 8% (30/371), 11% (12/111), 6% (1/18), and 14% (1/7), of category 0, 1, 2, 3, and 4 respectively.

Glomerulosclerosis by category was significantly associated with 1-year graft-failure on univariate analysis ($P = 0.04$) but not on multivariate analysis ($P = 0.36$). Frequencies of 1-year graft-failure by GS categories 0, 1, 2, 3, and 4 demonstrated a progressive increase in graft failure rates from 10% (9/90), 16% (61/371), 20% (22/111), 22% (4/18), to 29% (2/7), respectively, however the trend was not significant ($P = 0.30$).

There were 167 kidney transplants from ECD donors, and 30 exhibited MA. The outcome of kidneys from ECD donors correlated with the presence of MA. In patients with both these variables, 12 of 30 (40%) failed at 1 year, compared to 28 of 137 (20%) ECD kidneys without MA ($P = 0.02$). Frequencies of 1-year graft-failure by GS category in recipients of ECD kidneys did not show a trend in worse early graft failures [category 0 = 31% (4/13); 1 = 18% (18/98); 2 = 31% (14/45); 3 = 29% (2/7), and 4 = 50% (2/4), respectively ($P = 0.30$)].

Discussion

This study of histologically evaluated deceased-donor kidneys in single kidney transplant recipients evaluated several pretransplant baseline covariates relating to the donors and recipients. The independent predictors of graft failure were advanced recipient age, prior kidney transplant, ECD status (or donor age ≥60 years), DGF, and donor biopsy evidence of any vascular luminal narrowing ≥25% (arteries and/or arterioles). Other biopsy characteristics such as donor biopsy findings of ≥25% vascular luminal narrowing of the arterioles (separately), arteries (separately), 25–50% interstitial fibrosis, and GS by category were not independent predictors of graft failure 1-year post-transplantation, however, there was a trend toward significance for arteriosclerosis ≥25%. Additionally, the presence of arteriosclerosis (and arteriolosclerosis) correlated with increasing degrees of GS. Type II error may account for the absence of a significant difference for moderate arteriosclerosis and in the

higher categories of GS as only 8% and 4% of the sample exhibited moderate arteriosclerosis and >20% GS, respectively. The low frequency of kidney transplantation from donors with >20% GS reflects a change in practice patterns after our previous finding of poor early outcomes in this subgroup [10].

Donor vessel luminal narrowing has infrequently been evaluated for an association with graft outcome. Karpinski *et al.* [8], in a case–control study of 57 kidney transplants from 'high-risk' kidneys and 57 recipients of kidneys from 'low-risk' kidneys, observed that the incidence of DGF in recipients with a donor arterial or arteriolar wall thickness >50% than the diameter of the lumen ($n = 11$) was higher (100%) compared with in those recipients of kidneys from donors with a vessel 20–50% luminal narrowing (43%). Three studies did not find any associations of arteriosclerosis and/or arteriolosclerosis with graft dysfunction at 12 months [10–12]; however, in one report <3% [12] of the sample had moderate or severe vascular lesions, and in two studies the proportion of patients with moderate luminal narrowing was not elucidated [10,11]. Thus, it is not known if these studies had a sufficient sample size to assess the impact of moderate or severe chronic lesions.

Glomerulosclerosis has been variably identified as the critical parameter in graft outcomes in previous studies. Escofet *et al.* [9] identified percentage of GS and acute rejection, but not donor age, as independent predictors of glomerular filtration rate at 4 years on a multivariate linear regression analysis of 210 recipients with postperfusion biopsies. Randhawa *et al.* [10] found increasing histologic grades of GS to be associated with graft dysfunction at 12 months in a multivariate proportional odds model of 78 histologically evaluated kidney transplant recipients. Pokorna *et al.* [12] prospectively evaluated 200 recipients of single donor kidneys 18% of which were affected by ≥20% GS and 2% with arteriolar luminal narrowing of more than 1/3 of the lumen. However, on multivariate analysis, neither parameter emerged as a significant variable for early or late function estimated by 24-h creatinine clearance.

Although age and clinical parameters are useful in predicting graft outcomes, such as that proposed to define the ECD kidney [20], there is considerable individual variability in the magnitude of histologic changes related to age and medical conditions such as hypertension and diabetes [22]. In our study 90/129 (70%) of donors aged 60–78 had 0–9% sclerotic glomeruli (undoubtedly related to selection bias). Conversely, Escofet *et al.* [9] noted that 13% of donors <55 were found to have >10% GS, and in the current study moderate arteriosclerosis was present in 3/65 (5%) of biopsies from donors aged 30–39. The latter finding is analogous to the occurrence of arteriolar hyalinosis in 25- to 34-year-old subjects in an autopsy study, where it was considered to be a marker for early onset atherosclerotic disease [23].

Although our study was not designed to evaluate the utility of dual kidney transplantation (DKT), transplantation of both donor kidneys into one recipient to provide sufficient nephron mass to the recipient and thereby improve outcomes may be the preferred route for kidneys with chronic lesions. In the aforementioned prospective, case-controlled study by Remuzzi *et al.* [7], 124 single kidney transplants (SKTs) from donors >60 years of age that were not biopsied were compared to 54 DKTs and eight SKTs from donors >60 years of age that were biopsied and allocated for single or dual transplantation based on a 12-point histologic scoring system [7]. The graft failure rate at follow-up of at least 1 year (median 20, 26, and 13 months respectively) was significantly higher among nonbiopsied SKTs (23%) when compared to biopsied DKTs (6%), highlighting the benefit of utilizing biopsy criteria in kidneys from donors >60 years of age to decide on single or dual transplantation. Prospective studies with larger numbers of histologically evaluated ECD and otherwise high risk kidneys and longer follow-up times are needed to define criteria that maximize donor utilization and outcomes.

In summary, we found that renal allograft and patient survival after transplantation is inversely proportional to the chronic changes in the donor biopsy. The presence of ≥25% luminal vascular narrowing in particular is an independent risk factor for worse graft survival post-transplantation. In this subgroup, there was a 71% graft survival at 1-year post-transplantation and progressively worsening graft survivals at 3- and 5-year post-transplantation of 58% and 40%, respectively. Additionally, increasing degrees of GS, particularly over 20%, portends poor outcomes.

One of the most limiting factors in a study such as this one, where the objective is to find the pivotal risk factors for decision making in acceptance or refusal of donors, is that one can only evaluate risk factors in kidneys and recipients, which were actually selected for transplantation. Our study is also limited by the single-center study population and its retrospective nature. A potential limitation of any pretransplant biopsy is sampling bias. Both GS and arterionephrosclerosis may be patchy in distribution, and so may be under- or over-represented in a small sample.

Authorship

LKK: performed analysis, wrote paper, collected data. RM: collected data. AB: collected data. RS: paper design. PR: paper design, data collection.

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