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## Histological analysis of pre-transplant deceased donor renal biopsies and its association with long-term graft survival and function

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### ABSTRACT

**Background:** Pre-implantation kidney biopsy is a diagnostic tool used for deciding whether to accept an expanded-criteria deceased donor graft. However, the study of histopathological lesions in renal compartments as prognostic factors for graft function and survival has led to conflicting results.

**Objectives:** This study aimed to evaluate the presence of chronic lesions in pre-implantation kidney biopsies and correlate the findings with graft function and survival at 1, 3, and 5 years post-transplantation.

**Patients and Methods:** Around 430 kidney biopsies from standard and expanded-criteria deceased donors were analyzed between 2006 and 2013 at the hospital Santa Casa de Porto Alegre. Lesions were graded according to the Banff criteria. The glomerular filtration rate (GFR) was calculated by the CKD-EPI equation. Graft survival was calculated by the Kaplan-Meier method. Clinical variables related to graft outcome were assessed by Cox regression analysis.

**Results:** The decrease in graft survival and function at the analyzed periods was related to a greater degree of chronic lesions in renal compartments. Glomerulosclerosis (GS) was an independent risk factor for graft loss.

**Conclusions:** Chronic lesions in any renal compartment should be taken into account in the clinical decision of accepting the kidney, but a greater weight should be given to GS. Kidney recipients with more than 25% GS had a less favorable outcome in our study.

### *Implication for health policy/practice/research/medical education:*

This research has an implication for health practice assisting physicians in the management of critically ill patients with end-stage renal disease who require a renal graft to maintain life.

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### 1. Background

End-stage renal disease is the irreversible stage of kidney failure, requiring dialysis or transplantation for patient survival. Renal transplantation is the best substitutive treatment for advanced kidney disease as it is a cost-

effective therapy that improves survival and life quality. The insufficient number of donors in relation to the increasing number of patients on the waiting list causes an increase in the acceptance of expanded-criteria donor organs, as defined by the Organ Procurement

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and Transplantation Network/United Network Organ Sharing (OPTN/UNOS). In this context, renal biopsy is a tool used to define whether or not to accept expanded-criteria donor grafts (1-3). Literature data regarding the relationship between histopathological lesions and the prognosis of transplantation provide conflicting results. Therefore, this study evaluated how chronic lesions in the glomerular, interstitial, tubular, and vascular compartments of the kidney correlate with graft survival and function at one, three, and five years after transplantation.

## 2. Patients and Methods

### 2.1. Study population

This is a retrospective cohort study including 430 renal transplant recipients whose surgery procedures and pre-implant biopsies were performed at the Hospital Santa Casa de Misericórdia, a Transplantation Center at Porto Alegre, Southern Brazil, from January 2006 to December 2013. Donors were categorized as standard (SD) or expanded criteria (ECD) according to OPTN/UNOS definitions. Biopsies were performed surgically by the wedge technique. The histological analysis was performed using formalin fixation and conventional histological processing of 3-micron thick sections and included three slides stained with hematoxylin and eosin, one with Masson's trichrome, one with periodic acid-Schiff (PAS), and one with periodic acid-Schiff methenamine (PASM).

Morphological analyses were performed by a nephropathologist. Glomerulosclerosis (GS), interstitial fibrosis, tubular atrophy, and arteriosclerosis were scored according to the semi-quantitative Banff classification (2);

- GS: absent (<5%), mild (6%–25%), moderate (26%–50%), severe (>50%).
- Arteriosclerosis; absent (0%), mild (<25%), moderate (26%–50%), severe (>50%).
- Interstitial fibrosis; absent (<5%), mild (6%–25%), moderate (26%–50%), severe (>50%).
- Tubular atrophy; absent (0%), mild (<25%), moderate (26%–50%), severe (>50%).

The glomerular filtration rate (GFR) was estimated by the CKD-EPI equation at 1, 3, and 5 years post-transplantation.

Graft survival was calculated by the Kaplan-Meier method at 1, 3, and 5 years after kidney transplantation. The following variables were analyzed in the study as factors associated with graft loss: donor and recipient age and gender, standard or expanded criteria donor, presence of donor-specific antibodies (DSA) by the

recipient, number of HLA-A/B/DR mismatches, class I and II panel reactive antibodies, occurrence of delayed graft function, occurrence of acute rejection episodes in the first year post-transplantation, cold ischemia time, and type of immunosuppressive therapy. Variables were analyzed by univariate and multivariate statistical methods using the Cox regression model.

### 2.2. Ethical issues

1) The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained; and 3) This study was approved by the Ethics Committee of Universidade Federal de Ciências da Saúde de Porto Alegre (ethical code 495.047).

### 2.3. Statistical analysis

Statistical analysis was performed using the SPSS® (Porto Alegre, Brazil) version 20 software. Quantitative variables were presented as mean and standard deviation. Association of categorical variables was performed by the chi-square test, Fischer's exact test, and continuous variables by analysis of variance (ANOVA), adopting a significance level of  $P < 0.05$ . ROC curve analysis was used to establish the cut-offs of GS >25% and GFR <30 mL/dL. Kaplan-Meier method was used to graft survival. Cox regression model was performed for univariate and multivariate analysis.

## 3. Results

Table 1 presents the clinical and demographic characteristics of donors and recipients. Approximately 60% of the donors and recipients were male, with a mean age of about 50 years. The ratio between SD and ECD donors was approximately 1:1 (SD = 49.3%, ECD = 50.7%). In the first year post-transplantation, 41.6% of the recipients suffered an acute rejection episode, 14.2% had DSA, and 64.9% had delayed graft function.

Table 2 shows data on the lesions in renal compartments according to the Banff criteria.

The number of glomeruli identified in the biopsies ranged from 6 to 145. Biopsies showing less than 10 glomeruli that could significantly represent the tubulointerstitial and artery compartments were included in the study but did not have the glomerular compartment evaluated or included in the results. Biopsies that had artifacts in the interstitial and tubular compartments as a result of the intraoperative frozen section examination were not evaluated in relation to these compartments. Twenty-six biopsies did not show a good representation of the arteries.

The predominant results in all compartments were the

**Table 1.** Clinical and demographic data

All patients (n=430)	
Age, years (min-max)	52 (18-87)
Female gender (%)	167 (38.8)
Cause of ESRD (%)	
GN	26 (6.1)
DM	61 (14.2)
Hypertension	66 (15.3)
Other	277 (64.4)
Transplant number (%)	
= 1	386 (89.8)
> 1	44 (10.2)
Donor age (y)	51 (4-79)
Type of donor (%)	
SCD	213 (49.5)
ECD	217 (50.5)
CIT (%)	
< 12 h	8 (1.9)
12-24 h	218 (50.7)
>24 h	180 (41.9)
Unknown	24 (5.6)
DGF (%)	279 (64.9)
HLA mismatch, median (IQR)	4 (0-6)
PRA class I (%)	
0	231 (53.7)
1-49	155 (36.1)
50-79	25 (5.8)
>80	19 (4.4)
PRA class II (%)	
0	239 (55.7)
1-49	160 (37.3)
50-79	17 (4.0)
>80	13 (3.0)
DSA present (%)	60/415 (14.8)
Induction therapy	
Anti-CD25	265 (61.6)
ATG	91 (21.2)
No	47 (10.9)
eGFR mL./min/1.73 m <sup>2</sup>	
1 year mean (SD) n=351	40.6 (16.1)
3 years, n=164	45.8 (20.5)
5 years, n=63	42.7 (17.6)
Rejection, No. (%)	179 (41.6)
Median follow-up, mon (IQR)	54.6 (28.7-76.3)

ESRD= end stage renal disease, GN= glomerulonephritis, DM= diabetes mellitus, SCD= standard criteria donor, ECD= expanded criteria donor, CIT= cold ischemia time, DGF= delayed graft function, PRA= panel reactive antibodies, DSA= donor specific antibodies, ATG= anti-thymocyte globulin, eGFR= estimated glomerular filtration rate, IQR= interquartile range.

absence of lesions or mild chronic lesions. Only one biopsy showed severe GS (>50%), and this recipient lost the graft in the first year post-transplantation. Twelve biopsies showed severe arteriosclerosis. No transplanted kidney had severe interstitial fibrosis or tubular atrophy. Figure 1 shows graft survival in relation to renal compartments at 1, 3, and 5 years after transplantation.

**Table 2.** Histopathological donor biopsies data

	n=430	%
GS		
None	212	49.3
Mild	194	45.1
Moderate	18	4.2
Severe	1	0.2
Not evaluated	5	1.2
Arteriosclerosis		
None	129	30.0
Mild	176	40.9
Moderate	87	20.2
Severe	12	2.8
Not evaluated	26	6.1
Interstitial fibrosis		
None	211	49.1
Mild	192	44.7
Moderate	17	4.0
Not evaluated	10	2.3
Tubular atrophy		
None	121	28.1
Mild	278	64.7
Moderate	19	4.4
Not evaluated	12	2.8

Table 3 shows the results of GFR in relation to renal compartments at 1, 3, and 5 years post-transplantation. Table 4 shows the analysis of risk factors for graft loss. The multivariate analysis (Cox regression) revealed the following factors as independently influencing graft survival (hazard ratio [95% CI]): GS (1.05 [1.02–1.07]);  $P < 0.001$ , presence of DSA (1.88 [1.05–3.35];  $P = 0.03$  and the occurrence of rejection (1.80 [1.11–2.93]),  $P = 0.01$ .

The 25% GS cutoff for graft loss had AUC-ROC of 0.61 [95% CI 0.54-0.68];  $P = 0.003$ , a sensitivity of 14.5% and a specificity of 97.5%. The 25% GS cutoff for prediction of a GFR below 30 ml/min at one year showed the AUC-ROC of 0.63 [95% CI 0.56-0.69];  $P < 0.001$ , a sensitivity of 3.5% and a specificity of 98.0%.

#### 4. Discussion

The present study evaluated 430 pre-implantation biopsies of renal compartments according to the Banff criteria. The scores of each compartment were not added since the classification does not include the sum of score per item. The semi-quantitative Banff grading systems were the most frequently used according to a systematic review that evaluated 47 studies correlating histopathological scores and transplantation prognosis (3), but the weight given to each component, combined into a composite score, varied among studies. Several scores have been proposed to evaluate renal lesions

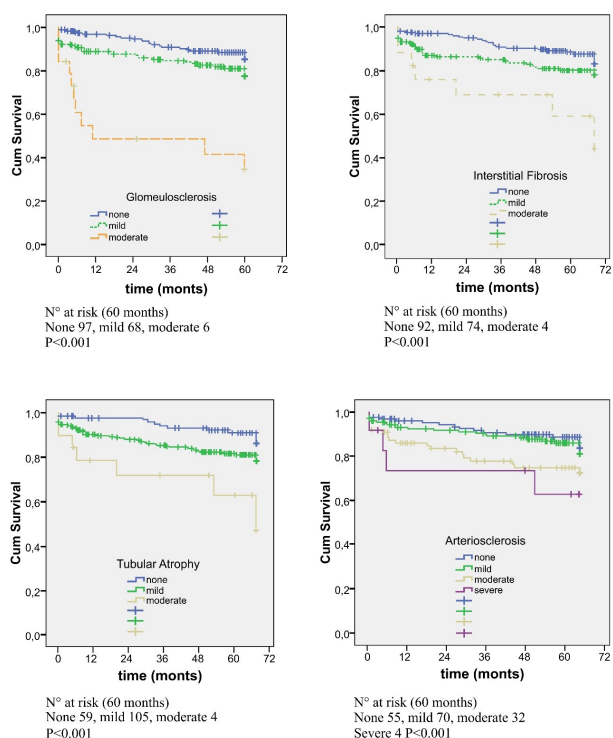


Figure 1. Graft survival curves.

globally, and the most common are the Pirani-Remuzzi score (4) and the Maryland Aggregate Pathology Index (MAPI) (5). This variation in methodology may explain the conflicting results of the literature.

Our study showed a significant difference in graft survival at 1, 3, and 5 years post-transplantation between the different degrees of histopathological lesions in renal compartments. Regarding GS, graft survival was about 50% at one and three years and less than 45% at five years, when the percentage of sclerosed glomeruli was greater than 25% (moderate lesions). On the other hand, in the absence of GS or mild GS (less than 25%), the survival curves remained above 80% for all the analyzed periods. Gaber et al suggested in 1995 that a cut-off of 20% GS was associated with adverse prognosis (6). Bajwa et al (7) showed that a GS greater than 5% was associated with graft failure, whereas Ciccirelli et al (8) observed this same outcome associated with a GS greater than 10%. Other studies reported the association of different GS cut-off values with graft loss (9,10), whereas some studies found no association between them (11-15). Sung et al did not report GS as an independent risk factor for graft loss (16). Likewise, Edwards et al found no association between a GS greater than 20% and post-transplant graft loss (17).

The area under the ROC curves for graft loss and GFR below 30 mL/min with 25% GS were 0.613 and 0.628,

respectively, showing a moderate discriminatory capacity, low sensitivity and high specificity. This result was slightly lower than the reported by a study that found an area under the curve of 0.7–0.8 for 20% GS (1).

We observed a reduction in graft function as the chronic lesions in all renal compartments increased. At one year post-transplantation, the mean GFR of 44.43 mL/min for GS below 5% decreased to 36.72 mL/min when GS was in the range of 6–25% ( $P < 0.001$ ) and to 31.64 mL/min when GS was in the range of 26%–50% ( $P = 0.75$ ). At 3 years, the mean GFR for the absence of GS dropped from 52.23 mL/min to 39.62 mL/min for mild GS ( $P < 0.001$ ) and to 33.18 mL/min for moderate GS ( $P = 0.067$ ). At five years, the reduction of GFR was not significant, and we attributed this result to the small number of patients who remained in the cohort. GFR significantly decreased as the degree of arteriosclerosis increased at 1, 3, and 5 years post-transplantation. The statistical power was small when comparing the group with severe arteriosclerosis due to the small number of cases in this category (8 patients). The interstitial and tubular compartments showed a significant inverse association of chronic alterations with graft function at 1 and 3 years post-transplantation, and, at 5 years, an inverse association between absence of lesions and mild lesions.

The present study is in agreement with the conclusions of Escofet et al and Randhawa et al (18, 19), which showed a reduction in GFR with the increase in GS at 4 years and 1 year post-transplantation, respectively. On the other hand, Koppelstaetter et al (20), Pokorna et al (13), and Arias et al (10) did not find an independent association between GS and graft function at 1, 2, and 3 years post-transplantation, respectively. Lu et al (15), Oda et al (21), and Szanya et al (22) found an association between arteriosclerosis and GFR, but four other studies reported no association between these parameters (10,20,23,24). Few studies report an association between chronic tubulointerstitial damage and graft function. Arias et al, Cockfield et al, and Koppelstaetter et al found no association between chronic tubulointerstitial damage and graft function at 6 months, 1 year, and 3 years post-transplantation (10,11,20).

As limitations of our study, we highlight the lack of a global chronicity score; as previously mentioned, this study strictly adopted the Banff criteria. We adopted the assumption that chronicity in any anatomical compartment is a prognostic factor as a justification for the compartmentalized analysis (2). Biopsies with moderate and severe alterations accounted for a small number of the samples in our study, as they are generally

**Table 3.** eGFR according donor biopsies compartments alterations

	GS			Arteriosclerosis			Interstitial Fibrosis			Tubular Atrophy		
	n	CKD-EPI	P	n	CKD-EPI	P	n	CKD-EPI	P	n	CKD-EPI	P
1 year												
None	182	44.433	0x1=.000;0x2=.075	112	46.094	0x1=.002;0x2=.000	187	44.314	0x1=.000;0x2=.002	111	46.538	0x1=.000;0x2=.000
Mild	157	36.716	1x2=.075	146	39.120	0x3=.064	146	36.794	1x2=.200	220	38.206	1x0=.000;1x2=0.70
Moderate	8	31.643		67	34.970	1x2=.426;1x3=1.0	11	27.825		12	27.744	
Severe	-	-		8	31.484	2x3=1	-	-		-	-	
Total	347	40.647		333	40.447		344	40.594		343	40.536	
3 years												
None	84	52.231	0x1=.000;0x2=.067	54	56.058	0x1=.001;0x2=.001	85	51.905	0x1=.000;0x2=.357	49	54.421	0x1=.000;0x2=.216
Mild	74	39.623	1x2=1	66	42.925	0x3=.002	70	38.623	1x2=1	106	41.971	1x2=.001
Moderate	6	33.181		31	39.799	1x2=1;1x3=.340	6	39.271		6	39.271	2x0=.216;2x1=1
Severe	-	-		7	28.774	2x3=.944	-	-		-	-	
Total	164	45.845		158	46.173		161	45.659		161	45.659	
5 years												
None	36	46.538	0x1=.138;0x2=1	16	52.736	0x1=.330;0x2=.062	31	49.447	P=0.12	17	49.259	P=.022
Mild	24	37.232	1x2=1	30	42.682	0x3=.260	30	36.256		44	40.526	
Moderate	3	40.708		11	35.521	1x2=1;1x3=1	1	40.016		1	40.016	
Severe	-	-		4	33.591		-	-		-	-	
Total	63	42.715		61	43.432		62	42.912		62	43.270	

eGFR, estimated glomerular filtration rate.

**Table 4.** Risk factors for graft loss

Cox regression univariate analysis for graft loss								
	No. of patients/events			Hazard ratio (95% CI)		P		
Donor age				1.02 (1.01 to 1.04)		0.002		
DSA (yes)				1.78 (0.86-3.71)		0.12		
GS%	430/72			1.05(1.03 to 1.07)		<0.001		
Fibrosis moderate	17/7			4.15 (1.81 to 9.54)		0.001		
Atrophy mild	121/13			1.91 (1.04 to 3.53)		0.037		
Atrophy moderate	19/7			4.74 (1.88 to 11.92)		0.001		
Arteriosclerosis moderate	87/21			2.15 (1.12 to 4.12)		0.02		
Arteriosclerosis severe	12/4			2.56 (0.84 to 7.74)		0.09		
Rejection (yes)	179/40			1.90 (1.19 to 3.03)		0.007		
Cox regression multivariate analysis for graft loss								
	Hazard ratio (95% CI)			P				
DSA (yes)	1.88 (1.05 to 3.35)			0.034				
Glomerular Sclerosis	1.05 (1.03 to 1.08)			<0.001				
Rejection (yes)	1.83 (1.14 to 2.92)			0.01				
Risk for graft loss/levels of GS								
Faixas (n)	B	SE	Wald	Df	P	Exp (b)	Lower	Upper
0 (100)			26.112	3	0.000			
1%-5% (110)	0.661	0.433	2.329	1	0.127	1.937	0.829	4.530
6%-25% (194)	0.977	0.392	6.226	1	0.013	2.656	1.233	5.721
>25% (15)	2.368	0.490	23.367	1	0.000	10.680	4.088	27.899

refused for transplantation. There was no control of variability among pathologists. A small number of biopsies had one or more compartments that were not evaluated. The compartments that were not evaluated were excluded from the calculation of graft survival and function.

## 5. Conclusions

In summary, our study found a significant difference in the graft survival in the evaluated periods according to chronic lesions in all renal compartments, as well as an association with graft function. A donor age greater than 60 years was a risk factor for graft loss, but the distinction between SD and ECD donors showed no association with graft loss. Independent risk factors for graft loss were the presence of DSA, the occurrence of an acute rejection episode in the first year after transplantation, and the degree of GS.

The authors suggest that chronic lesions in any renal compartment must be taken into account in the clinical decision to accept the organ, but the greater weight in this decision should be given to GS. Kidney recipients with more than 25% GS had a less favorable outcome in our study.

## Limitations of the study

We highlight the lack of a global chronicity score, there was no control of variability among pathologists, and a small number of biopsies had one or more compartments

that were not evaluated.

## Authors' contribution

KP and EK: conception, design, data analysis, data interpretation, literature review and writing article. RK and CK: acquisition of data, data analysis. LP and EC: support on conception, design and critical revising of content.

## Conflicts of interest

The authors declare no conflict of interest.

## Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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