Histopathological analysis of pre-implantation donor kidney biopsies: association with graft survival and function in one year post-transplantation

Análise histopatológica de biópsias pré-implante de rim de doadores: associação com a sobrevida e função do enxerto um ano após o transplante

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Data de submissão: 09/12/2013.
Data de aprovação: 09/12/2013.

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DOI: 10.5935/0101-2800.20140029

Abstract

Introduction: Pre-implantation kidney biopsy is a decision-making tool when considering the use of grafts from deceased donors with expanded criteria, implanting one or two kidneys and comparing this to post-transplantation biopsies. The role of histopathological alterations in kidney compartments as a prognostic factor in graft survival and function has had conflicting results. **Objective:** This study evaluated the prevalence of chronic alterations in pre-implant biopsies of kidney grafts and the association of findings with graft function and survival in one year post-transplant. **Methods:** 110 biopsies were analyzed between 2006 and 2009 at Santa Casa de Porto Alegre, including live donors, ideal deceased donors and those with expanded criteria. The score was computed according to criteria suggested by Remuzzi. The glomerular filtration rate (GFR) was calculated using the abbreviated MDRD formula. **Results:** No statistical difference was found in the survival of donors stratified according to Remuzzi criteria. The GFR was significantly associated with the total scores in the groups with mild and moderate alterations, and in the kidney compartments alone, by univariate analysis. The multivariate model found an association with the presence of arteriosclerosis, glomerulosclerosis, acute rejection and delayed graft function. **Conclusion:** Pre-transplant chronic kidney alterations did not influence the post-transplantation one-year graft survival, but arteriosclerosis and glomerulosclerosis is predictive of a worse GFR. Delayed graft function and acute rejection are independent prognostic factors.

Keywords: biopsy; glomerular filtration rate; graft rejection; kidney transplantation; prognosis.

Resumo

Introdução: A biópsia renal pré-implante é uma ferramenta na decisão de utilização de enxertos de doadores falecidos com critérios expandidos, implantação de um ou dois rins e comparação com biópsias pós-transplante. O papel de alterações histopatológicas nos compartimentos renais tem mostrado resultados conflitantes como fator prognóstico na sobrevida e função do enxerto. **Objetivo:** Avaliar a prevalência de alterações crônicas nas biópsias pré-implante de enxertos renais e a associação dos achados com a função e sobrevida do enxerto em um ano pós-transplante. **Métodos:** Foram analisadas 110 biópsias entre 2006 e 2009 na Santa Casa de Porto Alegre, englobando doadores vivos, falecidos ideais e com critérios expandidos. A pontuação foi conforme critérios sugeridos por Remuzzi. A taxa de filtração glomerular (TFG) foi calculada pela fórmula MDRD resumida. **Resultados:** Não houve diferença estatística na sobrevida do enxerto de doadores estratificados conforme Remuzzi. A TFG apresentou associação significativa com os escores totais nos grupos com alterações leves e moderadas e nos compartimentos renais isoladamente, pela análise univariada. O modelo multivariado encontrou associação com a presença de arteriosclerose, glomeruloesclerose, rejeição aguda e retardo na função do enxerto. **Conclusão:** As alterações crônicas renais pré-transplante não tiveram influência na sobrevida do enxerto em um ano pós-transplante no nosso estudo. Arteriosclerose e glomeruloesclerose, em qualquer grau, são preditores de TGF pior no mesmo período. Retardo na função do enxerto e rejeição aguda são fatores prognósticos independentes.

Palavras-chave: biópsia; prognóstico; rejeição de enxerto; taxa de filtração glomerular; transplante de rim.

Introduction

Kidney transplantation is a therapy with a good cost/benefit ratio, and it increases the survival and quality of life of patients with end-stage kidney disease. In the United States it is estimated that the number of patients with chronic kidney failure who would benefit from a transplant is growing at a rate of 7 to 8% a year.[1] Currently, in Brazil, approximately 80,000 patients with chronic kidney disease are on dialysis. Only 1/4 of them obtain a transplant.[2] This is due mainly to the discrepancy in the number of patients on the waiting list, compared to the small number of available organs.[3]

Consequently, the criteria to accept kidneys for transplantation were extended, allowing the use of organs that would have been discarded a few years ago. This led to an increase in the number of kidney transplantations using grafts considered suboptimal, currently known in the literature as expanded criteria donors, according to the Criteria of the United Network for Organ Sharing (UNOS).[4-6] Pre-implantation biopsies play a major role in defining structural integrity and the functional reserve of kidney specimens.[7,8] Different algorithms based on histological parameters have been proposed to evaluate kidneys from expanded criteria donors.[8-11] In biopsies performed according to protocol, it is known that glomerulosclerosis, interstitial fibrosis and arteriosclerosis are associated with an inferior kidney function over the long term.[12,13]

This study aims at evaluating how far histological alterations at pre-implantation biopsy interfere with the clinical outcome of kidney transplantation and graft survival, in a retrospective cohort that includes live donors, deceased donors considered ideal and deceased expanded criteria donors. Clinical criteria that may contribute to the outcome, such as donor age, HLA compatibility, cold ischemia time, delayed graft function and episodes of rejection were also analyzed.

Method

One hundred and ten pre-implantation kidney biopsies of donors were analyzed at the Santa Casa de Misericórdia Transplantation Service in Porto Alegre. They were performed from January 2006 to August 2009. Twenty-seven biopsies were from live donors, forty-seven from ideal deceased donors and thirty-six from donors with expanded criteria according to UNOS.

The underlying disease of the recipients was systemic arterial hypertension (15.4%), familial disease (14.4%), glomerulopathy (13.6%), *diabetes mellitus* (9.0%), unknown (40%) and others (7.2%).

The immunosuppression scheme was mostly combined: 43.6% of the patients received Tacrolimus, 30.9% Cyclosporin, 90.0% Mycofenolate Mofetil, 0.9% Azathioprine and 10.9% m-TORi. Thirty-two patients (29.1%) included medications other than Calcineurin inhibitors in their immunosupression scheme. Another 30.1% were inducted with Basiliximab (23.3%) and Daclizumab (1.8%). Acute rejection episodes were treated with corticosteroid pulse therapy and the corticoresistant cases with OKT3 or Thymoglobulin.

The glomerular filtration rate at the end of the first year post-transplantation was calculated using the abbreviated MDRD (Modified Diet Renal Disease) formula for each recipient and correlated with the donor biopsy findings. The donors were also subdivided into live, ideal deceased and expanded criteria deceased. Donor age was stratified as below and higher or equal to 60 years. The glomerular filtration rate was also correlated to the number of HLA incompatibilities (0-6), time of ischemia (> or < 24 hours), episodes of acute rejection (Yes or No) and delayed graft function (present or absent).

The chi-square test was used to analyze categorical variables. The means between 2 groups were analyzed using the *Student t* test and the means between 3 groups were evaluated by analysis of variance (ANOVA). Graft survival was estimated using the Kaplan-Meier method and compared using the Log-rank test. To control confounding and evaluate factors associated with GFR, the multivariate linear regression model was applied with a Backward extraction criterion. The level of significance was considered significant with alpha error less than 0.05.

Histopathological evaluation

Biopsies of expanded criteria donors were sampled as a wedge and submitted to transoperative freeze test to evaluate organ viability. The live donor samples were obtained by needle biopsy and no frozen sections were performed.

All the samples were fixed in 10% formaldehyde and submitted to conventional histological processing. Biopsies without glomeruli were excluded from the study.

The biopsies were analyzed according to the criteria described by Remuzzi,[14] evaluating the degree of glomerulosclerosis, tubular atrophy, interstitial fibrosis and arterial and arteriolar thickening. The score of these variables was computed as follows: absence of alterations = 0 points; mild alterations (less than 20%) = 1 point; moderate alterations (between 20 and 50%) = 2 points; and marked alterations (more than 50%) = 3 points. The final score ranges from 0 to 12, mild histopathological alterations being those with a score between 0 and 3, moderate, between 4 and 6 and marked between 7 and 12.

Results

The study population consists of 110 kidney transplant recipients subdivided into 27 from live donors, 47 from deceased donors considered ideal, and 36 from deceased donors with expanded criteria. The donor characteristics and the general histopathological findings are shown in Tables 1 and 2.

As to the histopathological score, there was a significant difference between the total score of grafts from deceased donors and live donors. The percentage of deceased donors in the group of mild pathological alterations (0-3 points) was 44.6% (37 of 83 donors), while that of live donors was 85.2% (23 of 27 donors). Forty-one deceased donors (49.4%) met the criteria for moderate histopathological alterations (4 to 6 points) compared to 4 live donors (14.8%). Five deceased donors (6.0%) presented marked histopathological alterations (7 to 12 points) compared to none of the live donors (p = 0.001). The individualized scores of glomerulosclerosis, interstitial fibrosis, tubular atrophy and arteriosclerosis were also compared between live and deceased donors, and significant differences were identified in each isolated compartment.

The graft of ninety-seven of the 110 patients studied was still functioning one year post-transplantation. The distribution of these recipients according to the score obtained in the pre-implantation biopsy, and the mean glomerular filtration rate (GFR) for each group is shown in Table 3.

The cumulative survival of the graft one year after transplantation, of all the population studied, stratified according to the three groups of histopathological scores - mild, moderate and marked - (Figure 1A) was 90%, 88.9% and 60%, respectively (Log Rank p = 0.079). When only the cumulative survival of the graft with deceased donors was analyzed for the same groups (Figure 1B), the values were 83.8%, 90.2% and 60% (Log Rank p = 0.132). Cumulative survival of the graft with live donors was 100% and 75% in the mild and moderate groups, respectively (Log Rank p = 0.016).

The evaluation of the glomerular filtration rate one year post-transplantation, calculated by the abbreviated MDRD formula in the different groups according to the total number of points of the histopathological score, presented a statistically significant difference between the group with mild histopathological

Table 1 Characteristics of donors and recipients

	All donors (n = 110)	Deceased donors (n = 83)	Live donors (n = 27)	p
Donor age Mean/sd - (median)	46.99 ± 13.14 (48.00)	49.02 ± 13.57 (52.00)	40.74 ± 9.43 (41.00)	0.004
Donor sex (% male)	59 (53.6%)	47 (56.6%)	12 (44.4%)	0.189
Recipient Age mean/sd - (median)	46.01 ± 13.69 (50.00)	49.37 ± 12.06 (52.00)	35.67 ± 13.44 (33.00)	< 0.001
Recipient sex (% male)	72 (65.1%)	55 (66.2%)	17 (62.9%)	0.463
Time of cold ischemia (hs) mean/sd - (median)		20.54 ± 5.16 (20.50)	-	
Delayed kidney function (%)	63 (57.3%)	61 (73.5%)	2 (7.4%)	< 0.001
Acute rejection (%)	33 (30.0%)	25 (30.1%)	8 (29.6%)	0.583
HLA (nº antigens) mean/sd (median)	3.19 ± 1.23 (3.00)	3.12 ± 1.05 (3.00)	3.41 ± 1.69 (3.00)	0.298
Hypersensitized (%) panel > 50%	2 (1.8%)	2 (2.4%)	0	0.568
Criteria for borderlines		36 (43.3%)	-	

Table 2 Data on general histopathological alterations

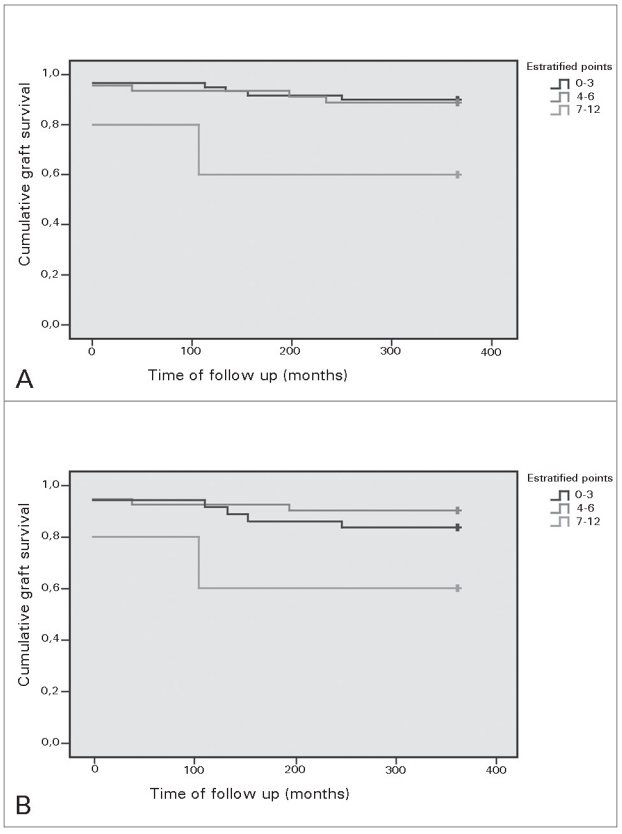
	Mean and SD	Median/Variation
Nº of Glomeruli	57.84 ± 33.54	51.50 (2-145)
Remuzzi Score	2.90 ± 2.13	3 (0-8)
Glomerulosclerosis	0.80 ± 0.64	1 (0-3)
Interstitial fibrosis	0.70 ± 0.56	1 (0-2)
Tubular Atrophy	0.65 ± 0.56	1 (0-2)
Vascular Stricture	0.78 ± 0.83	1 (0-3)

Table 3 Stratified score in the entire group and glomerular filtration rate one year after transplantation

Total score	N	%	GFR ml/min (m/sd)
Mild (0-3)[a]	54	55.67%	49.69 ± 16.91
Moderate (4-6)[b]	40	41.23%	40.69 ± 13.36
Marked (7-12)[c]	3	3.09%	44.30 ± 13.68

p = 0.006 a x b; p = 0.358 a x c; p = 0.698 b x c.

Figure 1. Graft survival according to the histopathological scores in transplants with live and deceased donors. Figure 1A: Log Rank p = 0.079 and with deceased donor grafts only; Figure 1B: Log Rank p = 0.132.



alterations (n = 54) and the group with moderate alterations (n = 40) (p = 0.006). There was no significant difference between the group with marked alterations and the others (Table 3).

When the GFR was compared among recipients of live donor grafts (n = 26, GFR = 54.26 +/- 14.52 ml/min) and from deceased donors (n = 71, GFR = 42.72 +/- 15.34 ml/min), independent of histopathological criteria, it showed a statistically significant difference (p = 0.001). When evaluated in the groups of deceased donors with expanded (n = 32, GFR = 38.23 +/- 13.20 ml/min) and ideal criteria (n = 39, GFR = 46.40 +/- 16.14 ml/min), the difference was also significant (p = 0.022).

Donor age was separated into less than and greater or equal to 60 years (n = 15, GFR = 36.26 +/- 14.84 ml/min) and in this way associated with the glomerular filtration rate. The GFR was significantly higher in the group under the age of 60 years (n = 82, GFR = 47.56 +/- 15.57 ml/min), (p = 0.011).

The presence of acute rejection and delayed initial graft function was statistically correlated with the GFR (p = 0.002 and 0.001, respectively). On the other hand the cold ischemia time and HLA incompatibilities did not present any significance.

Alterations in the kidney compartments evaluated (glomerulosclerosis, interstitial fibrosis, tubular atrophy and vascular fibro intimal thickening) were correlated singly with the kidney function (Table 4). No biopsy presented more than 50% glomerosclerosis and no transplant kidney had an interstitial fibrosis and tubular atrophy scores greather than 2.

The scores of glomerulosclerosis, interstitial fibrosis, tubular atrophy and arteriosclerosis were also grouped, each in two variables - absence of alterations or presence of alterations, the latter being the sum of the groups considered as mild, moderate and marked alterations. Considered in this way, the difference of the mean GFR among all groups was significant (p < 0.001; p = 0.001 and p = 0.002, respectively) The total score, likewise, was also stratified into two grade: mild alterations [(0-3), GFR = 49.69 +/- 16.91 ml/min] and moderate and marked [(4-12), GFR = 40.94 +/- 13.25 ml/min], (p = 0.005).

After adjustment using the multivariate model in the total sample, the variables that remained associated with GFR were arteriosclerosis (p = 0.038), presence of acute rejection (p = 0.005), delayed graft function (p = 0.024) and glomerulosclerosis (p = 0.029). Multivariate analysis was also performed only for the deceased donors, showing a significant correlation with arteriosclerosis (p = 0.010), acute rejection (p = 0.020) and delayed kidney function (p = 0.049).

Table 4 Points of the histopathological scores in the kidney compartments and kidney function one year after transplantation

	N	%	GFR (ml/min) (m/sd)	*p*
Glomerulosclerosis				
0[a]	32	32.9%	54.07 ± 15.21	$p < 0.001$ a x b; $p = 0.104$ a x c
1[b]	54	55.6%	40.98 ± 14.98	$p = 0.363$ b x c
2[c]	11	11.3%	45.50 ± 13.58	
Insterstitial Fibrosis				
0[a]	36	37.1%	52.99 ± 15.76	$p = 0.01$ a x b; $p = 0.118$ a x c
1[b]	57	58.7%	41.65 ± 14.82	$p = 0.878$ b x c
2[c]	4	4.1%	40.45 ± 11.36	
Tubular Atrophy				
0[a]	40	41.2%	51.93 ± 15.95	$p = 0.002$ a x b; $p = 0.167$ a x c
1[b]	54	55.6%	41.64 ± 14.69	$p = 0.790$ b x c
2[c]	3	3.09%	39.23 ± 14.68	
Arteriosclerosis				
0[a]	41	44.1%	52.08 ± 15.52	$p = 0.018$ a x b; $p = 0.001$ a x c
1[b]	36	38.7%	43.73 ± 14.84	$p = 0.171$ a x d; $p = 0.074$ b x c
2[c]	12	12.9%	34.63 ± 15.07	$p = 0.746$ b x d; $p = 0.457$ c x d
3[d]	4	4.3%	41.15 ± 12.82	

Discussion

This study is an analysis of biopsies from deceased donors with expanded criteria, ideal deceased donors and live donors. The biopsies of live donors were performed according to clinical study protocols.[15,16] All the deceased donors with expanded criteria in the study were submitted to biopsy with transoperative freezing to evaluate organ viability. Since it is a study of a retrospective cohort, the score and stratification into groups were performed after transplantation. The Remuzzi criteria were not used in the decision to utilize the kidney, nor in carrying out single or double transplantation. The decision to transplant was taken based on clinical data associated with chronic alterations identified and the degree of glomerulosclerosis (cutoff point 20%).

Five kidney biopsies in this study met the criteria to discard the organ according to Remuzzi (final score above 7). However, they were implanted as a result of less marked alterations in the transoperative freezing test and because one of them did not meet the expanded donor criteria. Two of these patients lost the graft, one of them never functioned and the other was lost to vascular thrombosis. Curiously, the three remaining patients did well, two with one year kidney function considered acceptable (56.1 ml/min; 47.5 ml/min and 29.3 ml/min).

The cumulative survival of the graft at one year post-transplantation was not different among the groups with mild, moderate or marked alterations in the total population, nor when only the survival of the deceased donors was evaluated. However, graft survival in the live donors was different among the groups with mild and moderate alterations, because of a loss that occurred among the four live donors with a moderate histopathological score. The recipient of this graft presented an episode of late acute rejection, which can be a confounding factor.

The variable considered as having the greatest impact on kidney function in one year was the distinction between live and deceased donors in univariate analysis. The mean GFR in live donors was 54.2 ml/min while in the deceased donors it was 42.7 ml/min ($p = 0.001$). This finding may suggest that immunoinflammatory alterations associated with death and cold ischemia time may be predictive of a worse outcome. It should also be added that live donors have a lower chronic damage score than deceased donors. Over half the live donors (55.6%) presented a normal histology against only 12.0% of the deceased donors ($p = 0.001$). In multivariate analysis the live donor variable did not present a statistical difference in GFR. This may be partly explained by the co-association of other factors particularly related to live donors, such as lower chronicity scores, age below 60 years, more

prevalent and low frequency of initial delay of kidney function. This co-association justifies our multivariate analysis performed separately in deceased donors. The mean GFR, among the ideal deceased donors and those with expanded criteria, was different statistically (around 8.2 ml/min lower in those with expanded criteria, $p = 0.022$), but we do not extratified histopathological scores between standard an expanded criteria donors because the small sample size. GFR was also different when compared to the variable age alone (above and below 60 years). On the other hand, in multivariate analysis, age above 60 years was not considered an isolated predictive factor of GFR. Yilmez *et al.*,[17] evaluating protocol biopsies for two years after transplantation, found that the chronic histopathological alterations at this stage were associated with age, both of the donor and of the recipient. According to Nankivell,[18] old age of the donor is strongly predictive of graft failure.

The presence of acute rejection in multivariate analysis was the most important variable associated with a worse mean GFR in the total population studied.

The correlation of GRF with the final histopathological score showed the difference between the groups (0-3) and (4-6). The mean of the former was more favorable (49.7 x 40.7 ml/min), showing that patients with mild chronicity scores have a better outcome than patients with moderate scores. Against all logic, group (7-12) had a mean GFR similar to group (4-6), 44.3 ml/min, and there was no statistical difference compared to the others. Our main hypothesis for this result is based on the small number of cases in this group (only 3 patients), since kidneys with this score should not be grafted according to the criteria of Remuzzi. As described above, 2 of our 3 patients in this group presented a function close to the expected level in kidney graft recipients. Lehtonen *et al.*[19] documented that the chronicity score in pre-transplantation kidney biopsies is related to graft function and development of chronic rejection in a year. Snoeijs *et al.*,[8] in a study with 199 donors above the age of 60 years showed that preexisting chronic damage was more important than the other clinical parameters in the transplantation outcome. Arias *et al.*,[20] in a multivariate analysis, showed that chronic alterations in all compartments were associated with worse graft survival. On the other hand, Lubuska *et al.*[21] did not find a negative influence of histopathological alterations in long term graft functioning.

In our study, glomerulosclerosis showed a statistically significant association with kidney function one year post-transplantation with a 13.00 ml/min GFR difference between score 0 and score 1. In multivariate analysis, the presence of glomerulosclerosis was alone predictive of lower GFR in one year post-transplantation, in the total sample studied. For Escofet *et al.*,[22] patients with over 20% glomerulosclerosis had worse kidney function in one year. Bajwa *et al.*,[23] analyzing 12,129 pre-implantation kidney biopsies, noted that the presence of more than 5% glomerulosclerosis was associated with a more unfavorable outcome. On the other hand, Cockfield *et al.*,[24] in a study with 730 biopsies, did not show an independent association of glomerulosclerosis with the prognosis. Navarro *et al.*[25] showed that glomerulosclerosis greater than 10% was not an independent predictive factor for graft failure.

Our paper shows that interstitial fibrosis and tubular atrophy present higher GFR means in group 0 compared to the others, but significant only between groups 0 and 1, possibly due to the small number in group 2. When grouped into two variables (present or absent), the patients without fibrosis or tubular atrophy showed better kidney function in one year. This is not confirmed in the multivariate model. Sulikowski *et al.*[26] observed that the patients with a better initial graft function did not have interstitial fibrosis.

The number of biopsies evaluated in the arteriosclerosis item in our study is different from the others (93.0 x 97.0), since 4 biopsies did not include arteries and were excluded from this analysis. Four donors had marked arteriosclerosis, reaching the maximum score (3). When arteriosclerosis was absent, mild or moderate, it showed a significant association, inversely proportional to kidney function. This did not occur with the group of marked alterations, possibly because of the limited sample in this category. In the multivariate analysis of deceased donors, the presence of any amount of arteriosclerosis was the most important variable in the association with GFR and also showed a significant correlation when the live donors were included in the study. Kayler *et al.*,[12] in a multivariate analysis, found that moderate arteriosclerosis was a significant predictor of the transplantation outcome in donors with and without expanded criteria. For Cockfield *et al.*,[24] fibro-intimal thickening was associated with reduced kidney function in six months. In another study no correlation was found between arteriosclerosis and kidney function.

In brief, our study shows that recipients of kidneys from live donors do better, possibly due to other accompanying associations such as lower chronicity score, lower rate of post-transplantation dialysis and the donors' tendency to be younger. Pre-transplant chronic kidney alterations did not influence the one year graft survival, but the presence of any degree of arteriosclerosis is a worse prognostic factor in the graft function, one year post-transplantation, and it is the most impactful variable among the deceased donors. Our analysis did not show an independent association with donor age. The presence of acute rejection is the single predictive factor for a less favorable graft outcome. The authors make some considerations about the limitations of the actual study. We can not infer histopathological cutoff points due the small sample, a very small number of biopsies showed higher chronicity scores, which can interfere in the statistic tests, and the heterogeneous donors group sample can interfere in the multivariate analysis. Several histopathological chronicity scores are proposed; however, precise cutoff points in evaluating kidney viability have not been clearly determined and the decision to implant the graft should be evaluated individually, taking into account the histopathological findings and the other clinical parameters of donor and recipient. Remuzzi histopathologic criteria determine cutoffs points on the analysis of pre-implantation biopsies, and can suggest possible management for transplantation of kidneys from deceased donors. Although the criteria are easy to apply, its validity should be documented in more long-term studies. Even so, pre-implantation biopsy has a major prognostic role and should be performed also in selected live donors, since graft outcome in these donors may interfere with the pre-existing chronic alterations.

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