ORIGINAL ARTICLE

Histopathological evaluation of pretransplant donor biopsies in expanded criteria donors with high kidney donor profile index: a retrospective observational cohort study

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SUMMARY

There is no consensus on the allocation of renal transplants from expanded criteria donors (ECD). The Kidney Donor Profile Index (KDPI) is used without the need for pretransplant donor biopsies (PTDB). We explored whether PTDB based on Remuzzi Score (RS) allows identification of those marginal kidneys in the highest calculated KDPI risk group (>91%) that appropriate for single transplantation. A retrospective study was conducted of 485 consecutive kidneys procured from a single center and transplanted if the RS was ≤4. We compared 5-year kidney and patients survival between KDPI groups and between RS <4 or =4 in the highest KDPI group. The median KDPI (interquartile range) was 71 (66–76) for KDPI <80% (n = 77), 86 (81–90) for KDPI 81–90% (n = 82), and 97 (94–100) for KDPI >91% (n = 205). Patient survival at 5 years was 85.7%, 85.3%, and 76.09% (P = 0.058) and death-censored graft survival was 84.4%, 86.5%, 73.6% (P = 0.015), respectively for each KDPI group. In >91% calculated KDPI group, there were no differences in graft survival depending on the RS (<4 vs. =4) (P = 0.714). The implementation of PTDB based on RS used for allocation of organs with the highest KDPI range could support to the acceptance of suitable organs for single transplantation with good patient and graft survival rate.

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Key words
biopsies, expanded criteria donors, kidney donor profile index

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Introduction

The use of expanded criteria donors (ECD) is continuously increasing. Accurate assessment and evaluation of these donors and appropriate allocation to age-matched recipients is necessary to ensure good survival [1–3]. However, the clinical parameters used to evaluate and classify the quality of these organs have been debated over the last few years. Ten years ago, Remuzzi *et al.* [4] clearly stated that histological evaluation of the graft from ECD was needed to decide whether to allocate them as single or dual transplants or whether to discard them. Other transplant groups have also asserted the need for a pretransplant donor biopsy (PTDB) as part of the evaluation process [5]. Concomitantly, transplant centers using a renal perfusion machine instead of cold

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storage have incorporated the flux and resistance index as part of the information to be used in the decision process in ECD kidneys [6].

Nonetheless, these proposals have not been widely or systematically used because they are confusing, there is no consensus, and the decision to accept or reject ECD is mainly based on intracenter experience [7–12]. Moreover, some authors have reported that the use of PTDB or a renal perfusion machine to help decision-making in marginal donors increases the rejection rate and is even considered the main cause of rejection of ECD kidneys [13].

More recently, many centers have adopted a simple allocation score, the Kidney Donor Profile Index (KDPI). One of the advantages of the KDPI is the absence of a PTDB and the reproducibility between different centers. Based on the Kidney Donor Risk Index (KDRI), this score represents the relative risk of post-transplant graft failure from a particular deceased donor compared with that of the average donor [14,15]. However, the use of the KDPI is associated with a high discard rate as KDPI tends to be high in diabetics or donors with cardiovascular risk without regard of the duration of diabetes or whether the kidney is actually affected by diabetes or other cardiovascular factors. In many centers, the cutoff of the KDPI score is at >85% for discard which could be reduced by the implementation of PTDB [16,17].

Our center has been systematically using the PTDB to accept or reject ECD kidneys based on the Remuzzi score (RS): accepting kidneys with an RS $\leq$4 and discarding those with an RS $\geq$5 or sometimes referring them to dual transplant centers.

Due to the lower allograft survival rates of ECD kidneys, we offer ECD transplants to older recipients according to an old-for-old policy [18]. ECD grafts can effectively meet the survival expectations in elderly patients, allowing younger functional kidneys with better long-term prognosis to be offered to young recipients.

The objective of our study was to explore whether using the RS for systematic PTDB evaluation, the usual method of ECD assessment in our hospital, allows identification of those marginal kidneys in the highest calculated KDPI risk group (>91%) that appropriate for single transplantation.

Methods

Patients and study design

This was a retrospective observational cohort study of PTDB from ECD transplants at a single center. KDPI was retrospectively calculated. From January 2000 to December 2010, a total of 311 consecutive ECD were detected at Hospital Clinic in Barcelona. Follow-up was conducted for 5 years. In our center, ECD were defined as donors older than 60 years or aged 50–59 years with at least two of the following conditions: a history of hypertension, serum creatinine >1.5 mg/dl or cause of death from cerebrovascular accident. Extraction of clinical and pathological information from the patients' medical records and reporting of these data were approved by the Ethics Review Board of Hospital Clinic in Barcelona.

Clinical data

Anthropometric and biochemistry data were extracted from clinical charts and from the database implemented at the same center for routine clinical care. Kidney graft function was evaluated by recording serum creatinine, estimated glomerular filtration rate (eGFR ml/min/1.73 m^2), and proteinuria at 1 and 5 years. Outcome was defined as death with a functioning graft or as an irreversible loss of graft function with the need to maintain or resume dialysis. Delayed graft function (DGF) was defined as the need for dialysis during the first week after transplant with subsequent recovery of renal function. Primary nonfunction (PNF) was defined as the absence of renal function because of technical failure during follow-up. Indication biopsies were taken if there was deterioration of graft function. The KDPI index was calculated retrospectively using the open source calculator [15]. The KDPI scoring system was based on 10 deceased-donor variables (age, weight, height, creatinine, ethnicity, hypertension, diabetes, cause of death, HCV-positive donor, and donation after cardiovascular death), with no donor having donation after cardiovascular death characteristic.

Biopsy evaluation

Wedge biopsies of both kidneys were obtained after removal of donor kidneys and sent to the pathology department for immediate pretransplant evaluation, using frozen sections (FS). All biopsies were prepared and read at the same pathology laboratory (Hospital Clínic Barcelona) 7/7 days and 24/24 h availability by the on-call pathologist, who could be any of the 10 different pathologists in our department, nine of whom were specialists in an area of pathology other than renal pathology and one of whom was a specialist in renal pathology. Agreement between observers and techniques

was evaluated using Kendall's Tau b correlation coefficient in a previously published paper by our group [19].

Three-micron-thick hematoxylin and eosin-stained FS were evaluated. All sections were evaluated for the number of glomeruli and the percentage of global glomerulosclerosis, interstitial fibrosis, tubular atrophy, and vascular narrowing. The degrees of interstitial fibrosis, tubular atrophy, and vascular narrowing damage were graded from 0 to 3, using the Remuzzi score (RS) definition [4]. For interstitial fibrosis and tubular atrophy, 0 corresponded to no lesion, 1 to 1–20% of parenchyma involved, 2 to 20–50%, and 3 to >50%. For vascular narrowing, 0 corresponded to no lesion, 1 to wall thickness less than diameter of the lumen, 2 to wall thickness equal to diameter of the lumen, and 3 to wall thickness greater than diameter of the lumen. Glomerulosclerosis was categorized using a modified RS into grades 0, 1, 2, and 3, corresponding to 0%, 1–20%, 21–30%, and more than 30% global sclerosis, respectively. Final RS was obtained by the sum of the scores of the four items. Kidneys with a final RS score ≤4 were allocated as single transplants and those with RS >4 score were rejected or referred to another center.

Allocation system

Allocation of each kidney was based on a software algorithm (Nefrolink®) taking into account high immunological risk patients, donor–recipient age matching, time of dialysis, and time on waiting list.

Immunosuppression in recipients

Basiliximab (Simulect®) induction (20 mg; 2 doses) or polyclonal (rabbit antithymocyte globulin; thymoglobuline) antibodies (7 daily doses of 1.25 mg/kg, adjusted according to lymphocyte count) were applied depending on prior immunological sensitization, cross-matching, and the potential recipient's historical and current panel reactive antibody (PRA) titters. Maintenance immunosuppression included tacrolimus (trough level 5–10 ng/ml), mycophenolate sodium (1080–1440 mg/day) or mycophenolate mofetil (1500–2000 mg/day), an mTOR inhibitor (trough level 5–10 ng/ml), and prednisone (5 mg/day). Calcineurin inhibitor therapy was minimized or avoided when possible in the elderly transplants. Later adjustments of maintenance immunosuppressants were performed during follow-up and were based on biopsy data or clinical events.

Statistical analysis

Data are expressed as means ± standard deviation or range as appropriate. The Kolmogorov-Smirnov test was used to assess the normal distribution of the variables. Between-group comparisons were carried out using the Mann–Whitney *U*-test, chi-square test, Fisher test or Wilcoxon *Z*-test, as appropriate, and correlations were explored using Spearman's coefficient. Univariate analysis was carried out with Kaplan–Meyer (KM) and log-rank test. Multivariable regression models included the KDPI variables: age, gender, weight, height, ethnicity, hypertension, diabetes, serum creatinine, and HCV. Recipient characteristics included: age, gender, BMI, primary renal disease, hypertension, diabetes, time on dialysis, number of renal transplant, cold ischemia, HCV, P.R.A, mismatch, DGF, PNF, AR, induction, and maintenance immunosuppression.

Cox regression model was estimated to examine the relationship between RS variables (glomerulosclerosis, tubular atrophy, interstitial fibrosis, arteriolar sclerosis), KDPI groups, and outcome. The significance level was established as 0.05. SPSS version 17.0 (SPSS System, Chicago, IL, USA, 2008) was used for statistical analysis.

Results

Donor characteristics

A total of 311 ECD were generated in our hospital from 2000 to 2010 and 485 kidneys were extracted for transplant. Of these, 72.8% were transplanted in our center ($n = 364$), 8.4% ($n = 42$) were transplanted in other centers, and 15.8% ($n = 79$) were discarded because of the sum of donor clinic characteristics and the pathology report.

Donor characteristics are shown in Table 1. All biopsies with a RS over 4 were rejected for transplantation in our center following RS criteria. Three-quarters (76.5%) of the donors were older than 60 years and 23.4% were 50–59 years old and had two risk factors to be considered ECD. In the transplanted group, 35 patients (38.4%) from the 81 to 90 KDPI calculated group presented a KDPI <85. The characteristics of discarded donor kidneys showed a higher number of older male donors with high KDRI. The median calculated KDPI and interquartile range (IQR) was 71 (66–76) for KDPI <80%, 86 (81–90) for KDPI 81–90%, and 97 (94–100) for KDPI 91–100%. There were no differences between groups in cardiovascular risk or in renal function.

Table 1. Donor and allograft characteristics based on pretransplant donor biopsy.

	Transplanted (*n* 406) RS ≤ 4	Discarded (*n* 79) RS > 4	*P*-value
Age (years)	65 ± 8	69 ± 7	<0.001
Gender (male, %)	52.2	71.9	0.003
Weight (kg)	74.89 ± 13.5	79.17 ± 10.2	0.002
Height (m)	1.67 ± 0.8	1.7 ± 0.89	0.004
BMI (kg/m^2)	27 ± 3	26.9 ± 3	0.783
Ethnicity (White, %)	95.81	94.93	0.839
Hypertension (%)	73.7	79.4	0.33
Diabetes (%)	21.5	31.7	0.068
SerumCreatinine (mg/dl)	1.14 ± 0.55	1.19 ± 0.47	0.229
HCV status (%)	7.1	7.9	0.487
CV death (%)	100	100	1
CIT (h)	16.29 ± 5	–	
KDPI			
KDPI <80 (%) (*n*)	20 (81)	6.3 (5)	0.009
KDPI 81–90 (%) (*n*)	22.4 (91)	16.5 (13)	
KDPI 91–100 (%) (*n*)	57.6 (234)	77.2 (61)	
PTDB based on RS			
Glomerulosclerosis (%)			
0	16.7	2.5	
1	69.5	36.7	
2	9.1	32.9	
3	4.7	27.8	0.001
Tubular atrophy (%)			
0	53.7	13	
1	45.6	74	
2	0.7	11.7	
3	0	1.3	0.016
Interstitial fibrosis (%)			
0	64.3	28.6	
1	34.5	58.4	
2	1.2	13	
3	0	0	0.010
Arteriolar sclerosis (%)			
0	62	10.3	
1	34.7	64.1	
2	3	19.2	
3	0.2	6.4	<0.001

BMI, body mass index; HCV, hepatits C virus; CV, cerebrovascular death; CIT, cold ischemia time; KDRI, kidney donor risk index; KDPI, kidney donor profile index; PTDB, pretransplant donor biopsies; RS, Remuzzi Score.

Biopsy characteristics and histological score distribution

The RS distribution based on calculated KDPI allocation are shown in Fig. 1. The single renal transplant rate for each group based on PTDB was 94.2% (KDPI <80%), 92.4% (KDPI 81–90%), and 84.9% (KDPI >91%), respectively.

Regarding biopsies (Table 1), the median number of glomeruli in the evaluated specimens for frozen sections were 35 ± 18. None of the samples included less than 10 glomeruli, the 81% of the evaluated samples included more than 20 glomeruli. All rejected allograft presented more lesions in all analyzed parameters but specially showed more glomerulosclerosis and arteriolar sclerosis. Glomerulosclerosis of 21–30% was found in 9.1% and more than 30% in only 4.7% in transplanted allografts.

Recipient characteristics

Recipient characteristics are shown in Table 2. As we could not retrieve data from the 42 kidneys transplanted

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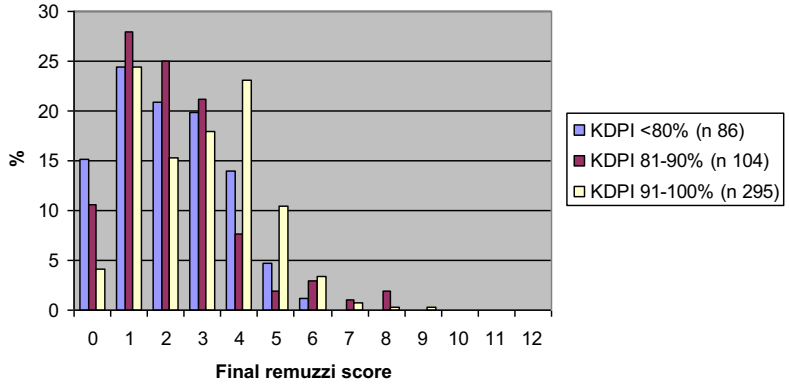

Figure 1 Pre-implantation donor biopsies based on Remuzzi Score allocation.

Food note: 485 Pre-transplant donor biopsies performed from ECD and classified according to calculated KDPI. Those with Remuzzi Score ≤ 4 were accepted for single transplant.

in other centers, we present only data from 364 kidneys transplanted in our institution. The group with the highest calculated KDPI had more elderly recipients but had spent less time on dialysis. A total of 23.9% ($n = 49$) had a KDPI of 100%. There were no differences between groups in cardiovascular risk, or immunological risk, PNF or DGF. The group with the lowest calculated KDPI had more HCV-positive donors. Recipients in the highest calculated KDPI group were induced with monoclonal antibodies in comparison with the other groups and calcineurin inhibitor therapy was minimized or avoided when possible. Regarding biopsies, only arteriolar sclerosis was significant higher in the highest calculated KDPI group ($P = 0.048$).

Renal function changes, DGF, and acute rejection

No differences were observed between groups in eGFR determinations at 1 year or at 5 years (Fig. 2). Patients in the higher calculated KDPI group with a pre-implant biopsy RS equal to 4 had an eGFR at 1 and 5 years of 38.15 ± 16 ml/min/1.73 m and 37.12 ± 17 ml/min/1.73 m and showed no differences with patients with an RS <4 40 ± 17 ml/min/1.73 m and 35.42 ± 17 ml/min/1.73 m² ($P = 0.491$; $P = 0.778$), respectively. There were no differences in the presence of proteinuria between groups at 1 year [259 (114–516) mg/dl, 238 (166–638) mg/dl, 342 (572–778) mg/dl ($P = 0.058$)] or at 5 years [209 (104–509) mg/dl, 192 (132–364) mg/dl, 241 (149–624) mg/dl ($P = 0.552$)], respectively. There were no differences between groups in DGF, and the incidence of acute rejection was similar across the groups (Table 2).

Patient and graft survival

All patients were followed up for 5 years. There were no differences in patient survival in KM-log rang test between calculated KDPI groups at any time point (Fig. 3a). The KDPI <80, 81–90, and >91 calculated group shows 90.9%, 93.9%, and 89.2% survival rate at one 1 and 85.7%, 85.3%, and 76.09% at 5 years, respectively. No differences were observed in cause of death. At 5 years, 38.9% died due to cardiovascular events, 36.2% from infectious events, 12.5% from tumors, 4.2% from hemorrhage, and 8.1% died from unknown causes.

Graft survival in the KDPI <80, 81–90, and >91 calculated groups was 88.3%, 89%, and 81% ($P = 0.098$), respectively at 1 year and was 75.3%, 73.2%, and 56.6% ($P = 0.002$) at 5 years (Fig. 3b). Death-censored graft survival in the KDPI <80, 81–90, and >91 calculated groups was 94.8%, 95.1%, and 90.2% at 1 year and was 84.4%, 86.5%, and 73.6% at 5 years, respectively. There were differences in graft survival between calculated KDPI groups at 5 years ($P = 0.015$) (Fig. 3c).

In the >91 calculated KDPI group, no differences were observed in death-censored graft survival between patients with a pre-implant biopsy RS of 0–3 ($n = 158$) vs. 4 ($n = 47$); $P = 0.714$ (Figs 4 and 5). In the highest calculated KDPI group, the causes of cumulative graft loss at 5 years were in the 45% ($n = 23$) due to chronic allograft nephropathy, 18.5% ($n = 10$) due to loss of follow-up, 14.8% ($n = 8$) due to primary nonfunction, 12.6% ($n = 7$) due to de novo glomerulonephritis or recurrence and 10.8% ($n = 6$) due to acute or chronic rejection.

Table 2. Recipient characteristics.

Transplanted in our center	*N* (364)	KDPI <80%[1] 77	KDPI 81–90%[2] 82	KDPI 91–100%[3] 205	*P*-value
Age (years)	62 ± 8	55 ± 8 [30–73]	59 ± 9 [31–85]	65 ± 7 [46–81]	<0.001[123]
Gender (male, %)	52.4	54.5	65.5	57.4	0.943
BMI (kg/m^2)	25.87 ± 4.4	26.76 ± 4.9	25.31 ± 4.3	25.7 ± 4.1	0.215
Hypertension (%)	89.2	86.8	87.7	90.6	0.585
Diabetes (%)	18.3	18.2	16	19.2	0.824
Primary disease					
Hypertension (%)	22.9	16.9	21	20.7	0.307
Diabetes (%)	14.2	11.7	12	12.3	
ADPKD (%)	17.7	18.2	23	15.3	
Glomerulonephritis (%)	19.1	16.9	22	18.2	
Interstitial (%)	3.6	13	4.9	8.4	
Unknown (%)	19.7	19.5	14.8	21.7	
Other (%)	2.8	3.9	2.4	2.5	
Time on dialysis (years)	3.8	3 [1.5–6]	3 [2–5]	2.5 [2–4]	0.02[13]
Number of renal transplant (%)					
1	81.8	77.9	78.3	84.8	0.242
2	15.5	15.6	20.5	13.2	
3	2.8	6.5	1.2	2	
HCV status (%)	11.2	23.7	15.7	4.5	0.001[123]
CMV status (%)	88.5	85.5	92.8	87.9	0.331
P.R.A > 25%	11.4	16.9	12	8.9	0.178
HLA Mismatch = 4 (%)	20.8	29	16.7	13.8	0.513
Cold Ischemia time (h)	16.2 ± 4.9	16.63 ± 4.5	16.16 ± 5.38	16.01 ± 5	0.495
Immunosuppression					
Thymoglobulin/ATG (%)	24.9	34.2	20.7	19.8	0.001[123]
Basiliximab (%)	52	39.5	56.1	65.5	
No induction (%)	21.4	26.3	23.2	14.7	
CNI (%)	72.3	81.5	67	68.5	
MPA (%)	92.5	89.5	93.9	94.1	
mTOR-i (%)	28	21	31.7	31.5	
DGF (yes %)	27.3	27.3	32.9	22.3	0.174
PNF (yes %)	2.6	2.6	2.5	2	0.946
Acute rejection (yes %)	22.3	16.9	24.2	23.4	0.436

Table 2. Continued.

Transplanted in our center	*N* (364)	KDPI <80%[1] 77	KDPI 81–90%[2] 82	KDPI 91–100%[3] 205	*P*-value
PTDB based on RS					
Glomerulosclerosis (%)					
0	17.8	21.4	24.1	13.8	
1	78.9	77.1	70.9	83	
2	3.3	1.4	5.1	3.2	
3	0	0	0	0	0.082
Tubular atrophy (%)					
0	55.8	55.8	59.8	54.1	
1	43.7	44.2	37.8	45.9	
2	0.5	0	2.4	0	
3	0	0	0	0	0.732
Interstitial fibrosis (%)					
0	65.7	74	70.7	60.5	
1	33.2	23.4	29.3	38.5	
2	1.1	2.6	0	1	
3	0	0	0	0	0.065
Arteriolar sclerosis (%)					
0	64.5	67.1	79	57.8	
1	32.7	30.3	21	38.2	
2	2.5	1.3	0	3.9	
3	0.3	1.3	0	0	0.048

BMI, body mass index; ADPKD, adult dominant polycystic kidney disease; HCV, hepatitis C virus; MPA, mycophenolate acid; mTOR-i, mTOR inhibitors; KDPI, kidney donor profile index; KDRI, kidney donor risk index; CIT, cold ischemia time; h, hours; DGF, delayed graft function; PTDB, pretransplant donor biopsies; RS, Remuzzi Score.

The multivariable analysis of KDPI variables showed that age older than 60 years was a risk factor to predict recipient survival [HR 2.08; 95% CI, (1.265–3.516); $P = 0.004$] and was not involved in kidney survival or acute rejection events. No other donor KDPI score characteristics were involved in kidney or recipient survival. The multivariable analysis of recipient variables showed that recipient age [HR 1.062; 95% CI, (1.035–1.090); $P < 0.001$], the presence of type 2 diabetes mellitus [HR 2; 95% CI, (1.266–3.158); $P = 0.003$] present prior cardiovascular events [HR 1.75; 95% CI, (1.012–3.056); $P = 0.045$], time on dialysis [HR 1.051; 95% CI, (1.002–1.102); $P = 0.041$], and the presence of DGF [HR 1.85; 95% CI, (1.217–2.830); $P = 0.004$] was predictors of patient survival. The presence of DGF [HR 3.69; 95% CI, (1.953–6.994); $P < 0.001$] was also a predictor of graft survival. Immunosuppression was not a predictive factor.

The Cox regression analysis of PTDB based on RS parameters in relation to graft survival showed that only interstitial fibrosis was related to graft survival in all calculated KDPI groups. glomerulosclerosis [HR 1.393; 95% CI, (0.483–4.017); $P = 0.050$], tubular atrophy [HR 1.715; 95% CI, (0.877–3.351); $P = 0.288$], interstitial fibrosis [HR 3.063; 95% CI, (1.556–6.030); $P = 0.005$], arteriolar sclerosis [HR 1.366; 95% CI, (0.675–2.766); $P = 0.069$].

Discussion

Our study shows that the systematic use of PTDB based on RS for allocation of organs with the highest KDPI range (>91%) could support the acceptance of suitable organs for single transplantation with good patient and graft survival rates.

The KDPI score is currently the most popular allocation score in the United States (US) because its component variables are known at the time of donation and because it has good reproducibility between different centers. However, this score has not been validated in other countries and the major limitation of the KDPI could be its applications in settings other than the United States.

Some centers that use the KDPI score to decide whether to accept or reject kidneys systematically reject donors with an extremely high KDPI score (>85%), and the rate of discarded kidneys remains very high [20]. Despite a clear relationship between high KDPI and graft failure, there is no evidence that programs accepting higher-KDPI kidneys would not adversely affect program evaluations [21]. In Spain, 32.4% of donors in 2015 were 70 years or older, and only 46.8% were younger than 60 years [22], while in the United States only 5% of donors whose kidneys were transplanted in 2014 were older than 65 years [23]. Because of this high percentage of older donors, the KDPI of Spanish donors can be estimated to be more than 80% in more than half, and close to 100% in more than 30%. Due to these differences in donor's characteristics some centers continue to perform biopsies in organs with a higher KDPI according to their clinical experience in order to identify suitable marginal kidneys. However, another group has suggested that current tools to evaluate some viable discarded kidneys with a KDPI ≥80, such as PTDB and/or perfusate biomarkers from a renal perfusion machine, are not sufficiently accurate to assess marginal kidneys [24]. To improve the KDPI score and aid international comparisons, some authors have proposed the use of a kidney quality index based on known data on viability and survival [25].

The question arises of whether it is time to abandon the PTDB or whether it should be performed systematically in organs with a KDPI score >91% in order to find suitable kidneys for single transplantation.

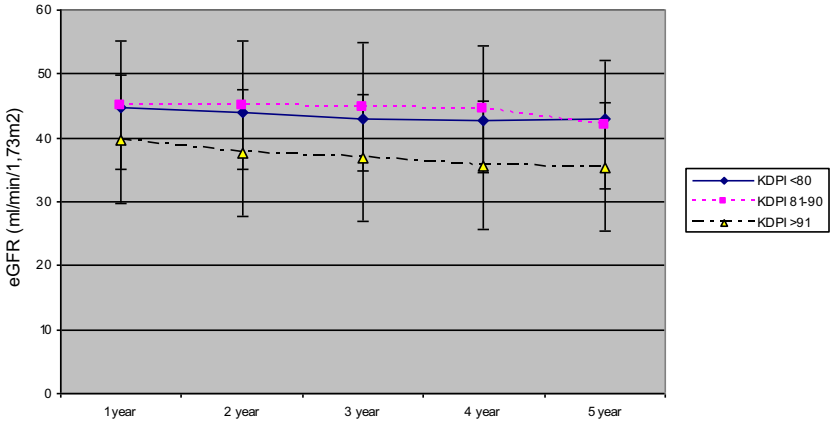

Figure 2 Renal function evolution.

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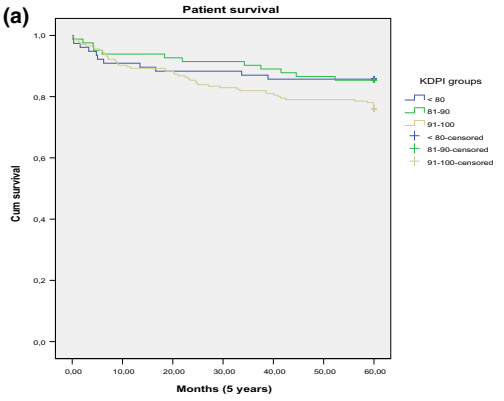
Despite the widespread use of pre-implantation biopsies, there is no consensus on their value in predicting allograft survival. Histological analysis continues to be the most common reason for nonacceptance of grafts [13]. Some of the limitations of the use of PTDB are discrepancies in the type of biopsy to use (wedge versus needle), in the histological technique (paraffin versus frozen) and in the interpretation of the lesions and reporting of the findings (particularly the percentage of glomerulosclerosis and the correlation with graft and patient survival), as well as in the widely recognized interobserver variability and the logistic requirements and cost of performing biopsies [5,7,10,11,19]. Wedge biopsies are generally preferred by surgeons in this setting, mainly because of better control of hemostasis. Wedge biopsy warrants an adequate number of glomeruli for evaluation, although other parameters could be better represented in a needle biopsy [26,27]. In our study, the technique used to perform PTDB was frozen section (FS). Even though RS was originally based on formalin-fixed stained sections, FS examination is employed in many institutions for decision-making because no inferiority to formalin-fixed and paraffin-embedded tissue has been demonstrated [5,19] and because it is a less expensive and faster technique than paraffin. Regarding the interpretation of lesions, studies are inconclusive about which biopsy parameters correlate with graft and patient survival, and the percentage of glomerulosclerosis does not justify the widespread use of biopsy for decision-making on whether or not to accept a kidney for transplantation. In our center, we apply a modified RS for glomerulosclerosis to better discriminate moderate (20–30%) from severe (>30%) glomerulosclerosis, although the impact of this modification is minimal, as only 4.7% of biopsies showed >30% of globally sclerosed glomeruli. Regarding concordance between observers in the evaluation of pre-implantational biopsies for selection purposes, interobserver variability produces more discrepancies than the technique used for sample processing; even so, these discordances had no significant impact on outcomes for the transplanted organs [5,19]. The same is true of the scoring system used for the PTDB: there is no standardized method. Remuzzi score criteria for the evaluation of lesions are slightly different from Banff criteria. Finally, the aim of biopsy evaluation is to identify organs with mild lesions that would have a favorable outcome, and this seems to be well accomplished both by Banff- and Remuzzi-based scores [5,16,27,28].

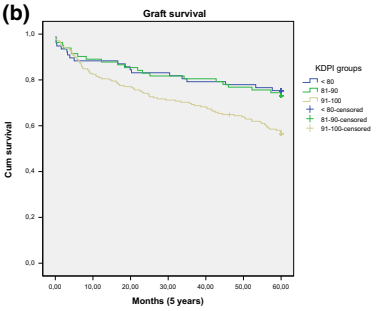
In some countries, performing PTDB based on RS would be impractical due to logistical concerns when

(a)



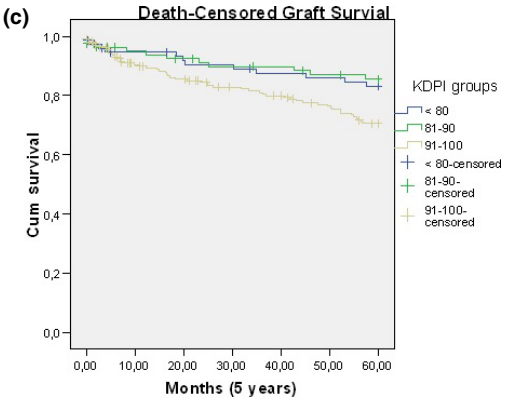
Number at risk	1 year	2 years	3 years	4 years	5 years
< 80% (n 77)	70	68	66	66	66
81-90% (n 82)	77	75	74	71	70
> 91% (n 205)	183	175	168	162	156
Long Rank Test	0.532	0.380	0.189	0.140	0.058

(b)



Number at risk	1 year	2 years	3 years	4 years	5 years
< 80% (n 77)	68	64	61	60	58
81-90% (n 82)	73	68	66	62	60
> 91% (n 205)	166	152	142	130	116
Long Rank Test	0,098	0,075	0,057	0,015	0,002

(c)



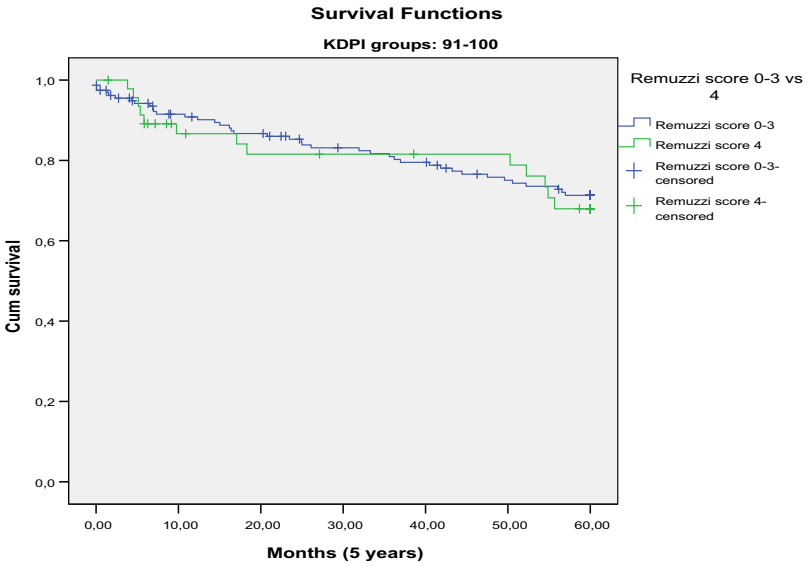
Number at risk	1 year	2 years	3 years	4 years	5 years
< 80% (n 77)	73	70	68	67	65
81-90% (n 82)	78	75	74	72	71
> 91% (n 205)	185	175	169	161	151
Long Rank Test	0,262	0,201	0,154	0,069	0,015

Figure 3 (a) Patient survival at 5 years. (b) Uncensored-graft survivat al 5 years. (c) Death-censored graft survival at 5 years.

kidneys are procured at a large distance from the transplanting center, but in terms of kidney recovery results, the availability of a centralized pathology service or scanned slides to read online should be considered [29].

Despite the described limitations, there are no prospective studies evaluating the PTDB versus KDPI score. Some retrospective studies have evaluated these score and have concluded that PTDB improves the acceptance rate in addition to the KDPI [16,17]. Gandolfini *et al.* [16] demonstrated the utility of PTDB in the highest KDPI range in addition to the KDPI score to reduce the discard rate. Despite a high allograft recovery rate reported in highest risk donors, kidneys with the highest KDPI score might have superior outcomes with a lower RS (<4) than those with a higher RS score (RS = 4) [16]. In our analysis, our single-center results of PTDB show a lower discard rate (19.8%) for the highest KDPI group and marginal kidneys with a RS of 4 allocated to single transplantation did not show lower graft or patient survival, previously described by other studies [28,30–32]. Our study also shows that the use of a relatively low threshold (RS $\leq$ 4) appears to be safe for single kidney transplantation and identifies good organs from donors with several risk factors that would otherwise be rejected. Of importance, dual kidney transplantation in ECD donors has recently been reported not offer greater advantages [33], while our results demonstrate the good functioning of single kidney transplantation with marginal kidneys.

Our center adopted the old-to-old allocation policy for marginal ECD transplants many years ago, thus avoiding allocation of ECD kidneys to recipients with



Number at risk	1 year	2 years	3 years	4 years	5 years
0-3 (n 158)	144	136	130	123	117
4 (n 47)	41	39	39	39	34
Long Rank Test	0,604	0,663	0,696	0,741	0,714

Figure 4 Graft survival in patients with a pre-implant biopsy Remuzzi score of 0–3 vs. 4 in the group with a kidney donor profile index (KDPI) score of 91–100%.

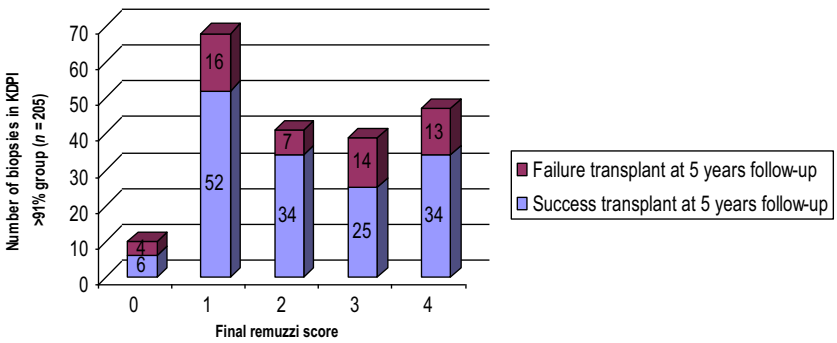


Figure 5 Remuzzi score in the group with the highest kidney donor profile index (KDPI).

longer life expectancies. Consequently, the results of our PTDB program are limited to elderly transplant candidates. Massie *et al.* [34] showed that transplanting kidneys with a KDPI score of 91–100 reduces the risk of mortality compared with remaining on dialysis and on the waiting list in the hope of receiving a lower KDPI kidney. Recently it has been published that pre-emptive or nonpre-emptive transplantation with a KDPI calculated score >85% was associated with lower mortality hazard after the first year compared with the waitlist in patients older than 60 years old concluding that further consideration should be given to increased utilization of high KDPI grafts in older patients with the goal of avoiding or limiting time on dialysis [35]. In very old patients (older than 70 years), the use of ECD kidneys is not a predictor of death or graft loss. Moreover, some groups have shown that allocating lower quality kidneys in older recipients attenuates the risk of graft lost [36–38]. In our analysis, we observed that only donor age older than 60 years was a significant variable for patient survival, and that DGF was the only variable that affected death-censored graft survival. Heldal *et al.* [39] also observed that donor age over 60 years, DGF, time on dialysis, and HLA antibodies were associated with greater death-censored graft loss in ECD transplants. Actions should be implemented to improve allocation in older patients and the management of DGF with the goal of improving patient and graft survival.

Our study has several limitations. First, KDPI was retrospective calculated according to the UNOS data of the previous year. Second, we did not calculate the estimated post-transplant survival score (EPTS) to select the allocation system, which was based on an old-to-old policy. We know that in other countries high KDPI range kidneys have to be discarded due to regulatory concerns regarding center outcomes and not kidney suitability. Neither there is in our center a comparison group accepted without PTDB. We did not provide baseline and follow-up data of recipients of ECD kidneys with RS > 5 referred to dual transplant centers. Other potentially limiting factors are the use of a calcineurin inhibitor-free immunosuppression regimen and other "center effect" variables that, although our single-center results are less dispersed, may limit extrapolation of results to other transplant groups.

In conclusion, our data suggest that PTDB based on RS in donors with a high KDPI, especially in KDPI >91%, provides useful clinical information for decision-making on accepting and allocating suitable kidneys for single transplants, with guarantees of good graft and patient survival despite the high calculated risk and the high RS. Organs with an RS equal to 4 and a KDPI of 100% also show good graft survival when transplanted as single grafts.

Authorship

AS-E: collected, analyzed clinical data and wrote the paper. AS: collected, analyzed histological data and did manuscript review. IR: data collection and manuscript review. LR: Data collection and manuscript review. DP: data collection and manuscript review. MM: data collection and manuscript review. FD: data collection and manuscript review. JMC: data collection and manuscript review. MS: study design and manuscript review. FO: study design and manuscript review.

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Conflict of interest

This work was an unsupported study. The authors have no conflicts of interest. The authors are responsible for the content and writing of the article. All authors have given signed consent for publication.

REFERENCES

1. Port FK, Bragg-Gresham JL, Metzger RA, *et al.* Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002; **74**: 1281.
2. Ojo AO, Hanson JA, Meier-Kriesche H, *et al.* Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol* 2001; **12**: 589.
3. Pascual J, Zamora J, Pirsch JD. A systematic review of kidney transplantation from expanded criteria donors. *Am J Kidney Dis* 2008; **52**: 553.
4. Remuzzi G, Cravedi P, Perna A, *et al.* Long-term outcome of renal transplantation from older donors. *N Engl J Med* 2006; **354**: 343.
5. Azancot MA, Moreso F, Salcedo M, *et al.* The reproducibility and predictive value on outcome of renal biopsies from expanded criteria donors. *Kidney Int* 2014; **85**: 1161.
6. Nicholson ML, Hosgood SA. Renal transplantation after ex vivo normothermic perfusion: the first clinical study. *Am J Transplant* 2013; **13**: 1246.
7. El-Husseini A, Sabry A, Zahran A, Shoker A. Can donor implantation renal biopsy predict long-term renal allograft outcome? *Am J Nephrol* 2007; **27**: 144.

8. Shapiro R, Halloran PF, Delmonico FL, Bromberg JS. The 'two, one, zero' decision: what to do with suboptimal deceased donor kidneys. *Am J Transplant* 2010; **10**: 1959.
9. European Renal Best Practice Transplantation Guideline Development Groups. ERBP guideline on the management and evaluation of the kidney donor and recipient. *Nephrol Dial Transplant* 2013; **28**(Suppl. 2): ii1.
10. Furness PN, Taub N. International variation in the interpretation of renal transplant biopsies: report of the CERTPAP Project. *Kidney Int* 2001; **60**: 1998.
11. De Vusser K, Lerut E, Kuypers D, *et al.* The predictive value of kidney allograft baseline biopsies for long-term graft survival. *J Am Soc Nephrol* 2013; **24**: 1913.
12. Wang CJ, Wetmore JB, Crary GS, Kasiske BL. The donor kidney biopsy and its implications in predicting graft outcomes: a systematic review. *Am J Transplant* 2015; **15**: 1903.
13. Sung RS, Christensen LL, Leichtman AB, *et al.* Determinants of discard of expanded criteria donor kidneys: impact of biopsy and machine perfusion. *Am J Trasplant* 2008; **8**: 783.
14. Rao PS, Schaubel DE, Guidinger MK, *et al.* A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation* 2009; **88**: 231.
15. Organ Procurement and Transplantation Network (OPTN): Kidney Donor Profile Index Calculator. https://optn.transplant.hrsa.gov/resources/allocation-calculators/kdpi-calculator/ Accessed June 2015.
16. Gandolfini I, Buzio c, Zanelli A, *et al.* The kidney donor profile index (KDPI) of marginal donor allocated by standardized pretransplant donor biopsy assessment: distribution and association with graft outcomes. *Am J Transplant* 2014; **14**: 2515.
17. Tanriover B, Mohan S, Cohen DJ, *et al.* Kidneys at higher risk of discard: expanding the role of dual kidney transplantation. *Am J Transplant* 2014; **14**: 404.
18. Fritsche L, Horstrup J, Budde K, *et al.* Old-for-old kidney allocation allows successful expansion of the donor and recipient pool. *Am J Transplant* 2003; **3**: 1434.
19. Sagasta A, Sánchez-Escuredo A, Oppenheimer F, *et al.* Pre-implantation analysis of kidney biopsies from expanded criteria donors: testing the accuracy of frozen section technique and the adequacy of their assessment by on-call pathologists. *Transpl Int* 2016; **29**: 234.
20. Tso PL. Access to renal transplantation for the elderly in the face of new allocation policy: a review of contemporary perspectives on "older" issues. *Transplant Rev* 2014; **28**: 6.
21. Snyder JJ, Salkowski N, Wey A, *et al.* Effects of high-risk kidneys on scientific registry of transplant recipients program quality reports. *Am J Transplant* 2016; **16**: 2646.
22. http://www.ont.es/infesp/Memorias/Memoria%20donantes%202015.pdf.
23. Hart A, Smith JM, Skeans MA, *et al.* OPTN/SRTR 2015 Annual Data Report: Kidney *Am J Transplant* 2017 Jan; **17**Suppl 1: 21.
24. Doshi MD, Reese PP, Hall IE. Utility of applying quality assessment tools for kidneys with KDPI ≥80. *Transplantation* 2016; Epub ahead of print. https://doi.org/10.1097/tp.0000000000001388.
25. Pascual J, Pérez-Sáez MJ. Kidney donor profile index: can it be extrapolated to our enviroment? *Nefrologia* 2016; **36**: 465.
26. Haas M, Segev DL, Racusen LC, *et al.* Arteriosclerosis in kidneys from healthy live donors. Comparison of wedge and needle core perioperative biopsies. *Arch Pathol Lab Med* 2008; **132**: 37.
27. Losappio V, Stallone G, Infante B, *et al.* A single-center cohort study to define the role of pretransplant biopsy score in the long-term outcome of kidney transplantation. *Transplantation* 2014; **97**: 934.
28. Kosmoliaptsis V, Salji M, Bardsley V, *et al.* Baseline donor chronic renal injury confers the same transplant survival disadvantage for DCD and DBD kidneys. *Am J Transplant* 2015; **15**: 754.
29. Hass M. Donor kidney biopsies: pathology matters and so does the pathologist. *Kidney Int* 2014; **85**: 1016.
30. Carta P, Zanazzi M, Caroti L, *et al.* Impact of the pre-transplant histological score on 3-year graft outcomes of kidneys from marginal donors: a single-centre study. *Nephrol Dial Transplant* 2013; **28**: 2637.
31. Navarro MD, Lopez-Andreu M, Rodriguez-Benot A, *et al.* Significance of preimplantation analysis of kidney biopsies from expanded criteria donors in long-term outcome. *Transplantation* 2011; **91**: 432.
32. Mazzucco G, Magnani C, Fortunato M, Todesco A, Monga G. The reliability of pre-transplant donor renal biopsies (PTDB) in predicting the kidney state. A comparative single-centre study on 154 untransplanted kidneys. *Nephrol Dial Transplant* 2010; **25**: 3401.
33. Pérez-Sáez MJ, Montero N, Redondo-Pachón D, Crespo M, Pascual J. Strategies for an expanded use of kidneys from elderly donors. *Transplantation* 2017; **101**: 727. https://doi.org/10.1097/TP.0000000000001635.
34. Massie AB, Luo X, Chow EK, *et al.* Survival benefit of primary deceased donor transplantation with high-KDPI kidneys. *Am J Transp* 2014; **14**: 2310.
35. Jay CL, Washburn K, Dean PG, Helmick RA, Pugh JA, Stegall MD. Survival benefit in older patients associated with earlier transplant with high KDPI kidneys. *Transplantation* 2016; **101**: 867.
36. Molnar MZ, Streja E, Kovesdy CP, *et al.* Age and the associations of living donor and expanded criteria donor kidney with kidney transplant outcomes. *Am J Kidney Dis* 2012; **59**: 841.
37. Tullius SG, Tran H, Guleria I, *et al.* The combination of donor and recipient age is critical in determining host immunoresponsiveness and renal transplant outcome. *Ann Surg* 2010; **252**: 662.
38. Hernandez RA, Malek SK, Milford EL, Finlayson SR, Tullius SG. The combined Risk of donor quality and recipient age: higher-quality kidneys may not always improve patient and graft survival. *Trasplantation* 2014; **98**: 1069.
39. Heldal K, Hartmann A, Leivestad T, *et al.* Clinical outcomes in elderly kidney transplant recipients are related to acute rejection episodes rather than pretransplant comorbidity. *Transplantation* 2009; **87**: 1045.