ORIGINAL ARTICLE

Chronic histological changes in deceased donor kidneys at implantation do not predict graft survival: a single-centre retrospective analysis

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SUMMARY

The use of preimplantation kidney biopsies (PIKBs) to aid deceased donor kidney utilization decisions is controversial. Outcomes of transplants that had been biopsied after the decision had been made to implant were analysed, in order to determine the association between chronic histological changes at implantation and graft outcomes. A retrospective analysis of transplants between the year range 2006–2015 was performed. Karpinski scores on biopsies were collected, and graft outcomes were analysed using univariate and multivariable techniques. Also, Karpinski scores from single and dual kidney transplants from older donors were examined to determine if knowledge of the score preoperatively would have altered utilization. Four hundred and eight single kidneys were transplanted. Although kidneys with scores >4 had lower 1- and 3-year median (IQR) estimated glomerular filtration rates (eGFRs) than those scoring 0–4 (51 (37–66) vs. 35 (26–52) ml/min/1.73 m^2, $P < 0.001$, and 52 (34–64) vs. 35 (24–52) ml/min/1.73 m^2, $P < 0.001$, respectively), there was no significant association between Karpinski score and death-censored graft survival on univariate or multivariable analyses. The utilization analysis (75 single and 25 dual kidney transplant recipients) suggested that systematic use of PIKBs would have resulted in 29% fewer patients being transplanted. This analysis does not support the systematic use of PIKBs to determine deceased donor kidney utilization.

Transplant International 2019; 32: 523–534

Key words
biopsy, kidney transplantation, survival, utilization

Received: 27 September 2018; Revision requested: 13 November 2018; Accepted: 4 January 2019; Published online: 8 February 2019

Introduction

Deceased donor kidney transplant programmes are increasingly successful, with improving long-term outcomes [1,2] and falling waiting lists [2,3]. Significant challenges remain, however, including the need to more accurately match expected graft survival with recipient lifespan and thus ensure that organ utilization is optimized. Between 10% and 20% of kidneys from deceased donors are discarded [3–6], primarily because of concerns about organ quality and uncertainty about long-term graft survival.

Tools to predict graft outcome based on donor- and/or organ-related characteristics have been widely investigated [7]. Large retrospective registry analyses have identified deceased donor clinical characteristics, such as age and hypertension, which are associated with graft failure [8,9]. It would therefore seem reasonable to

doi:10.1111/tri.13398

assume that the presence of chronic histological changes within the donated kidney, such as those seen in older, hypertensive donors, would also be associated with poor graft outcomes.

Kidney biopsies to detect such changes can either be performed preimplantation (with the intention of waiting for emergency histological analysis to aid utilization decisions), or can be done after the decision to implant the organ has been made. The former, widely termed preimplantation kidney biopsies (PIKBs), are used extensively in the US, with almost 75% of kidneys from extended criteria donors being biopsied [10]. Surgical biopsies taken after the decision has been made to implant the kidney provide information on 'baseline' chronic changes, and are known as time-zero biopsies.

Preimplantation kidney biopsies are contentious, as the evidence-base for this approach is considered by some to be weak [11,12]. Their widespread use has been proposed as one of the underlying causes for the perceived high rate of kidney discard in the US [13,14]. Previous studies investigating the possible association between chronic renal histological changes at implantation and graft survival have often been small, used more than one biopsy technique, included both living and deceased donor kidney transplants, included a high proportion of younger deceased donors, or originated from centres that commonly performed PIKBs (thus biasing utilization decisions) (reviewed in ref. 11).

In order to determine whether chronic donor histological changes at the time of implantation were predictive of graft outcomes, we analysed a large cohort of single deceased donor kidney transplants that had undergone time-zero biopsies using a single technique. Biopsies were taken after the decision to implant the kidney had been made. This cohort reflects current UK deceased donor demographics, with increasing proportions of older donors, donation after circulatory death (DCD) donors, and those with significant co-morbidities [2,5,15]. Finally, a separate analysis of transplants from older donors was performed, including both single and dual adult kidney transplants (DAKT), retrospectively analysing how systematic use of PIKBs in this donor group might have impacted organ utilization.

Materials and methods

Study population

This was a retrospective observational cohort study at a single centre including all adult recipients of single kidney-only transplants from deceased donors aged over 10 years, between July 2006 and December 2015. Kidneys from donation after brain death (DBD) and controlled DCD donors were included. Between July 2006 and January 2012, immunosuppression consisted of basiliximab induction, oral cyclosporine, mycophenolate mofetil and prednisolone. From January 2012 onwards, oral tacrolimus replaced cyclosporine, and immunological risk at the time of transplantation was stratified according to presence of anti-human leucocyte antigen (HLA) antibodies, recipient ethnicity, and whether or not the recipient had received a transplant previously.

Kidney biopsies

Time-zero kidney biopsies were taken with a 16-gauge core biopsy needle by the operating surgeon after the decision had been made to implant the organ. Biopsy specimens were formalin-fixed and paraffin-embedded (FFPE); 29 sections were cut and nine slides prepared. The sections were stained with haematoxylin and eosin (12 sections on four slides), periodic acid-Schiff (nine sections on three slides), periodic acid silver methenamine and Masson's Trichrome (four sections on one slide for both stains). Occasionally, PIKBs were taken, though this was limited because of lack of availability of histopathology services outside working hours, and uncertainty about the evidence supporting their use.

All kidney biopsies were analysed within a week of transplantation by one of five renal histopathologists. A Karpinski (K) score was reported based on appearances within the glomerular, interstitial, tubular and vascular compartments; each component scoring between 0 (no chronic changes) and 3 (severe chronic changes), giving a total score between 0 and 12 [16]. The K score is essentially identical to the Remuzzi (or Pirani) score, differing only in minor definitions of vasculopathy and the number of glomeruli needed for adequacy [12,17]. Biopsies were considered inadequate if the sample contained <20 glomeruli, as previously described [16]; these kidneys were excluded from outcome analyses.

Clinical outcome measures and definitions

Recipients were followed for 5 years post-transplant or until January 2018, whichever occurred first. Donor risk was quantified using the UK Kidney Donor Risk Index (UKKDRI), consisting of donor age, weight, hypertension, duration of hospital stay and adrenaline usage [9]. Cold ischaemic time (CIT) was defined as the duration from cold perfusion in the donor to re-perfusion with the recipient's blood. Graft function was measured using

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the four-variable Modification of Diet in Renal Disease estimated glomerular filtration rate (eGFR) equation. Recipients with a failed graft were assigned an eGFR of 5 ml/min/1.73 m^2. Delayed graft function (DGF) was defined as the need for dialysis within 7 days post-transplant, regardless of cause. Death-censored graft survival (DCGS) was defined as the number of days from transplantation to the date of graft failure (i.e. return to long-term dialysis, or re-transplantation, whichever occurred first). Primary nonfunction (PNF) was defined as graft survival of zero days, regardless of cause.

Statistical analyses

Patients were grouped based on K score (i.e. low K score (0–4) vs. high K score (5–12)). This threshold reflects utilization scoring thresholds for single kidney transplants [18,19].

Differences in demographic or clinical characteristics between groups were examined using Kruskal–Wallis test or the Chi-squared test. Wilcoxon rank test was used for nonparametric paired data. All variables were first tested for normality using the Shapiro–Wilk test. Spearman's rho was used to assess correlation between continuous nonparametric data. Imputational techniques were not used for missing data; complete case analysis was employed as it was assumed that missing data occurred at random. Number and percentage of missing variable data was detailed in the appropriate tables. Kaplan–Meier survival curves were used to demonstrate DCGS and patient survival; differences between groups were examined using the log-rank test.

Multivariable analyses were performed to identify independent predictors of eGFR, DCGS and patient survival. Candidate variables. Donor and recipient variables available at the time of transplantation, as well as K score, were included in the multivariable analyses if $P < 0.10$ on univariate analyses. The variance inflation factor (VIF) was calculated for each covariate in the multivariable analyses; the covariate was removed if there was multicollinearity (defined as VIF ≥ 5) [20]. Linear regression was used to assess factors predictive of 1-, 3- and 5-year eGFR. Cox regression was used to assess factors predictive of DCGS and patient survival, and results were expressed as hazard ratios (HR) with 95% confidence intervals (CI), with P values derived from likelihood ratio tests. Data were analysed using IBM SPSS Statistics for Macintosh version 24 (IBM, Armonk, NY, USA). Two-sided tests were conducted and $P < 0.05$ was considered statistically significant.

Utilization analysis

In order to determine how routine usage of PIKBs might have altered organ utilization of kidneys from older donors in our unit, we retrospectively examined all kidney-only transplants from DBD or controlled DCD donors aged 60 years and over between 1 January 2012 and 31 December 2015. Organs were implanted as single or DAKT [21]. Our DAKT programme was initiated in early 2012; the decision to implant two kidneys as a DAKT was based on local criteria (Table S1). Kidneys that had received a PIKB were excluded from this analysis, as utilization decisions had been made on this basis.

K scores were examined retrospectively to determine how knowledge of these scores prior to transplantation might have impacted organ utilization, using scoring thresholds initially defined by Remuzzi *et al.* and then modified by others [18,19]. In those kidneys with adequate time-zero biopsies, the following algorithm was retrospectively applied to determine how organ utilization might have been affected:

- if only one kidney was accepted at our centre
  - and the K score was 0–4, then 'single kidney'
  - and the K score was 5 or above, then 'decline'
- if both kidneys were accepted at our centre
  - and both K scores were 0–4, then 'two single kidneys'
  - and the highest K score of the pair was 5 or 6, then 'DAKT'
  - and the highest K score of the pair was 7–12, then 'decline' both organs

DCGS and eGFRs for single kidney transplants and DAKTs were analysed, as above.

Results

Donor, recipient, operative and biopsy characteristics

During the study period, 765 deceased donor kidneys were implanted as single kidney-only allografts at our centre. Recipients where no time-zero biopsy had been performed ($n = 178$), or where the biopsy was inadequate for K scoring ($n = 179$), were excluded (Fig. 1). Of the 408 kidneys left for analysis, only one had had a PIKB. Median (IQR) follow-up was 1513 (1013–1971) days.

In the group with adequate biopsies ($n = 408$), median (IQR) donor age was 51 (41–60) years (Table 1). A high proportion of kidneys were from DCD donors ($n = 134$; 32.8%), or had stroke as the donor cause of death ($n = 241$; 59.1%). More than a third of donors

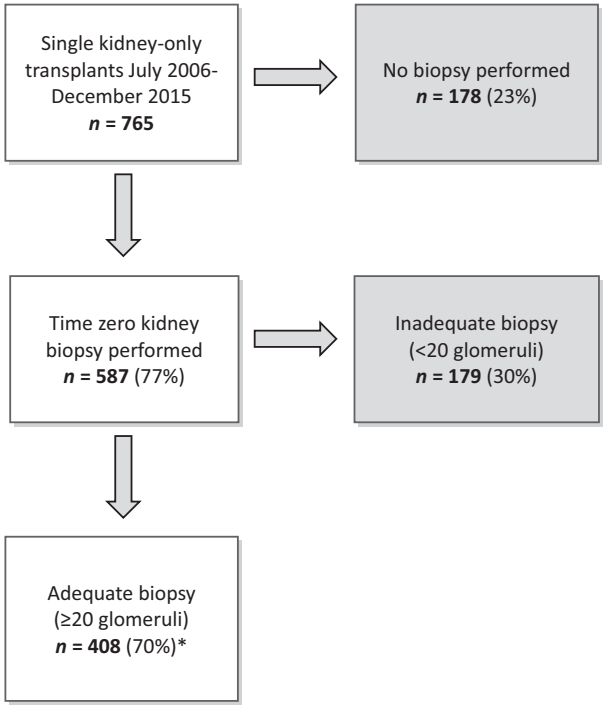

Figure 1 Flow diagram of kidney biopsies and study numbers. *Includes one kidney that had had a preimplantation kidney biopsies (PIKB).

fell into the 'high risk' United Kingdom Kidney Donor Risk Index (UKKDRI) quartile [9]. Importantly, the donor, recipient and operative characteristics between kidneys which were not biopsied and those with adequate biopsies were similar (Table 1).

Median (IQR) overall K score was 4 (2–5), with a range from 0 to 8 (Fig. 2). Almost one-third of kidneys had scores >4 (n = 129; 32%). As expected, there was a moderate positive correlation between donor age and K score (Spearman's rho r = 0.53, P < 0.001; Fig. 3).

When transplants were stratified into K score groups, kidneys in the higher K score group were more likely to be from older donors, DCD donors, have higher UKKDRIs, be implanted into older recipients, and be less well-matched for HLA than those in the low K score group (Table 2).

Graft function

There was a wide variation in post-transplant graft function when stratified by K score (Fig. S1A–C). There was no correlation between K score and eGFR at 1 and 3 years post-transplant on an unadjusted analysis (Spearman's rho r = −0.3). When grouped, kidneys with high K scores had significantly poorer eGFR at 1 and 3 years post-transplantation when compared to kidneys with low K scores, but did not reach statistical significance at 5 years (Table 3). The incidence of DGF did not differ significantly between the low and high K score groups in recipients of DBD donor kidneys (32.8% vs. 35.6%; P = 0.66), or DCD donor kidneys (43.6% vs. 40.8%; P = 0.76).

Linear regression analysis was used to find independent predictors of eGFR. Candidate variables were tested individually in univariate analyses (Table 4) before selection for multivariable analysis (Table 5). For every increment in K score, the analysis predicted a drop in eGFR by 4 ml/min/1.73 m^2 at 1 year. UKKDRI, donor female gender, re-transplantation, and CIT were all independently predictive of lower eGFRs at one or more of the follow-up time points.

Graft and patient survival

DCGS was 94% (n = 385), 92% (n = 377) and 89% (n = 366) at 1, 3 and 5 years post-transplantation. There was no statistically significant difference in DCGS when stratified by overall K score (P = 0.72; Fig. 4). Interestingly, even organs with apparently severe chronic histological changes at implantation (K score 6 and above) had DCGS of more than 80% at 5 years, though numbers were small. When comparing low and high K score groups, there was no statistically significant difference in DCGS (P = 0.26; Fig. 5). Individual components of the K score were also examined; there was no association between the interstitial (P = 0.64), tubular (P = 0.34), glomerular (P = 0.78) and vascular component scores (P = 0.30) with DCGS (Fig. S2A–D). Overall, the rate of PNF was 3.2% (n = 13). There was a lower rate of PNF in kidneys with a K score of 0–4 when compared to those that scored 5–8 (1.8% vs. 6.2%, P = 0.02).

Subgroup analyses were undertaken to determine if higher K scores were associated with worse DCGS in increased risk organs. There were no statistically significant differences in DCGS between kidneys with overall K scores 0–4 vs. 5–8 when only donors aged ≥50 years (n = 231), ≥60 years (n = 103) or UKKDRI >1.35 (n = 137) were analysed (Fig. S3A–C). Seven kidney transplants had K scores of ≥7; all grafts are still functioning.

Univariate Cox regression analysis of DCGS showed that only re-transplantation and UKKDRI had P < 0.10 (Table 6); K score did not. Re-transplantation and UKKDRI were therefore the only variables included in the multivariable analysis. Both re-transplantation and UKKDRI were independently associated with DCGS (HR (95% CI) 3.20 (1.61–6.37), P = 0.001; and 2.15 (1.03–4.51), P = 0.04, respectively).

Patient survival was 97% (n = 398), 95% (n = 386) and 93% (n = 379) at 1, 3 and 5 years post-

Table 1. Donor, recipient and operative characteristics of kidneys with an adequate biopsy and those kidneys not biopsied.

Variable	Adequate biopsy (n = 408)	No biopsy (n = 178)	P value
Donor age (years)	51 (41–60)	51 (42–59)	0.31
Donor gender (%)			
Male	210 (51.5)	96 (53.9)	0.58
Female	198 (48.5)	82 (46.1)	
Donor type (%)			
Donation after brain death	274 (67.2)	114 (64.0)	0.46
Donation after circulatory death	134 (32.8)	64 (36.0)	
Cause of death (%)			
Stroke	241 (59.1)	87 (48.9)	0.04
Trauma	40 (9.8)	17 (9.6)	
Other	127 (31.1)	74 (41.6)	
United Kingdom Kidney Donor Risk Index (UKKDRI)*	1.04 (0.97–1.46)	1.04 (0.94–1.47)	0.84
≤1.35	262 (65.8%)	111 (68.1%)	0.57
>1.35	136 (34.2%)	52 (31.9%)	
Recipient age (years)	51 (42–59)	59 (46–67)	0.06
Recipient gender (%)			
Male	258 (63.2)	108 (60.75)	0.56
Female	150 (36.8)	70 (39.3)	
Recipient ethnicity (%)			
White	232 (56.9)	96 (53.9)	0.52
Black	124 (30.4)	52 (29.2)	
Other	52 (12.7)	30 (16.9)	
Primary renal disease (%)			
Diabetes mellitus	41 (10.0)	23 (12.9)	0.36
Hypertension	73 (17.9)	25 (14.0)	
Other	294 (72.1)	130 (73.0)	
Graft number (%)			
1	344 (84.3)	148 (83.1)	0.73
>1	64 (15.7)	30 (16.9)	
HLA mismatch level*,† (%)			
1	55 (14)	14 (8.5)	0.21
2	130 (33)	48 (29.3)	
3	188 (47)	89 (54.3)	
4	26 (6)	13 (7.9)	
Cold ischaemia time (min)	835 (660–1027)	849 (709–1071)	0.15

Data are expressed as median (IQR) or number (%).

*Missing data (UKKDRI n = 30, HLA mismatch level n = 28).

†Defined according to the UK allocation policy for deceased donor kidneys and was based on donor-recipient differences at HLA-A, HLA-B and HLA-DR loci: level 1 was a mismatch of 000; level 2 was a 0 HLA-DR and a 0/1 HLA-B mismatch; level 3 was a 0 HLA-DR and a 2 HLA-B mismatch, or a 1 HLA-DR and a 0/1 HLA-B mismatch; and level 4 was a 2 HLA-DR or a 1 HLA-DR and 2 HLA-B mismatch.

transplantation. There was no association between K score and patient death (low versus high K score groups; P = 0.29). Patient survival was 99% (n = 275) in the low K score group and 95% (n = 122) in the high K score group at 1 year. At 3 years, patient survival was 95% (n = 265) in the low K score group and 94% (n = 121) in the high K score group. No candidate variables had $P < 0.10$ on univariate Cox regression analysis, including K score (data not shown).

Organ utilization analysis

The use of PIKB has been advocated to determine organ utilization, especially in deceased donors aged 60 years and over [18,21]. A cohort of such donors was analysed to determine whether knowledge of K scores prior to implantation might have altered organ usage.

Between 1 January 2012 and 31 December 2015, there were 75 single kidney transplants and 25 DAKT from

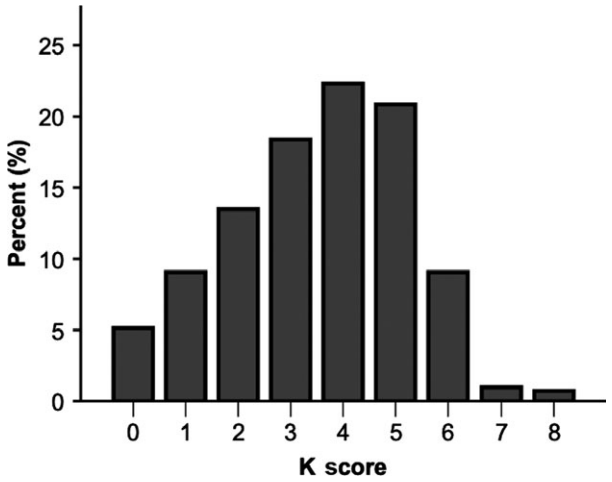

Figure 2 Distribution of Karpinski (K) scores in single kidney-only transplants from deceased donors (n = 408).

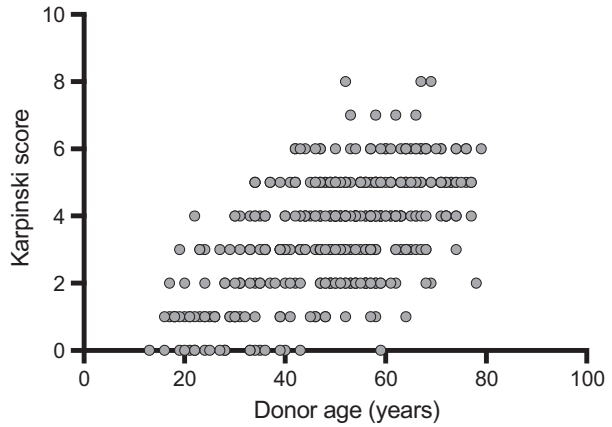

Figure 3 Deceased donor age versus Karpinski score (n = 408).

donors aged ≥60 years with adequate time-zero biopsies from all kidneys in our unit. Seventy-three single and six DAKT were excluded because of no/inadequate biopsy; four singles and seven DAKTs were excluded because of PIKB.

Using the algorithm described in the Materials and Methods, organ utilization decisions were re-analysed as if all K score results had been available preoperatively (Fig. 6). Use of PIKBs would have been expected to lead to fewer single kidney transplants (50 vs. 75 recipients), fewer DAKT (21 vs. 25 recipients). Overall, 29% fewer patients would have been transplanted. For single kidney transplants and DAKT, where application of the algorithm did not lead to a change of utilization group (i.e. knowledge of the K score preoperatively would not have altered the decision to implant as a single or dual transplant), graft outcomes were not significantly improved (Fig. S4, and Tables S2 and S3).

Discussion

This retrospective analysis examined the ability of a composite histological scoring system to predict outcomes in more than 400 deceased donor kidney transplants. Our study has demonstrated that overall K score was not associated with DCGS on either univariate or multivariable analyses. Even in subgroup analyses of older donors or those with high UKKDRI, and using different scoring thresholds, there was no observed association between K score and DCGS. Likewise, the glomerular, vascular, interstitial and tubular K score components did not impact on DCGS. Routine use of PIKBs in donors aged 60 years and over, with adherence to recommended scoring thresholds [18,19], would probably have resulted in a reduction in the number of transplanted recipients by almost 30%, with no apparent improvement in graft outcomes.

This study, with a high proportion of older and increased risk kidney donors, and using a single biopsy technique and optimal tissue preparation techniques [22], corroborates previous evidence that chronic changes present at implantation are not predictive of graft survival [11]. Use of PIKBs was rare in our study (<1%), reducing the risk of selection bias. Our findings cast doubt on the use of this scoring tool as a means of analysing PIKBs to aid organ utilization decisions. This is of particular interest given the imminent start of a stepped-wedge cluster randomized trial evaluating the impact of a national emergency PIKB service on the organ utilization of kidneys offered from deceased donors aged over 60 years (Pre-Implantation Trial of Histopathology In renal Allografts – PITHIA; ISRCTN11708741). The trial will give UK clinicians the option of selecting a PIKB or not; it will provide evidence on whether or not the use of PIKB alters organ utilization, but is not designed to determine whether or not chronic changes at the time of implantation influence graft survival.

Our results differ from similar retrospective analyses, including a recent publication from another UK group [18]. These discordant results are hard to explain, though differences in donor selection and/or biopsy technique should be considered. Although both studies had similar donor age profiles, the Cambridge group frequently used PIKBs, with 16% of single kidneys transplanted after urgent histological analysis [18]. This might have introduced selection bias, though it seems

Table 2. Donor, recipient and operative characteristics of the low K score group (K score 0–4) versus high K score (K score 5–8).

Variable	K score 0–4 (n = 279)	K score 5–8 (n = 129)	P value
Donor age (years)	49 (35–57)	58 (50–66)	<0.001
Donor male gender	143 (51%)	67 (52%)	0.92
Donor type (%)			
Donation after brain death	196 (70.3)	78 (60.5)	0.05
Donation after circulatory death	83 (29.7)	51 (39.5)	
Donor cause of death (%)			
Stroke	115 (41)	86 (67)	0.73
Trauma	32 (12)	8 (6)	
Other	132 (47)	35 (27)	
United Kingdom Kidney Donor Risk Index (UKKDRI)*	1.02 (0.83–1.28)	1.39 (1.01–1.85)	<0.001
Recipient age (years)	49 (40–58)	54 (46–63)	0.005
Recipient male gender	116 (42%)	92 (71%)	0.02
Recipient ethnicity (%)			
White	157 (56.3)	75 (58.1)	0.46
Black	90 (32.3)	34 (36.4)	
Other	32 (11.4)	20 (5.5)	
Primary renal disease (%)			
Diabetes mellitus	20 (10.8)	11 (8.5)	0.37
Hypertension	55 (19.7)	18 (14.0)	
Other	205 (69.5)	100 (77.5)	
Graft number (%)			
1	230 (84.6)	114 (89.8)	0.16
>1	42 (15.4)	13 (10.2)	
HLA mismatch level (%)*,†			
1	44 (16.2)	11 (8.7)	0.02
2	89 (32.7)	41 (32.3)	
3	127 (46.7)	61 (48.0)	
4	12 (4.4)	14 (11.0)	
Cold ischaemia time (min)	810 (641–1020)	866 (643–1011)	0.48

Data are expressed as median (IQR) or number (%).

*Missing data (UKKDRI n = 10, HLA mismatch level n = 9).

†Defined according to the UK allocation policy for deceased donor kidneys and was based on donor-recipient differences at HLA-A, HLA-B and HLA-DR loci: level 1 was a mismatch of 000; level 2 was a 0 HLA-DR and a 0/1 HLA-B mismatch; level 3 was a 0 HLA-DR and a 2 HLA-B mismatch, or a 1 HLA-DR and a 0/1 HLA-B mismatch; and level 4 was a 2 HLA-DR or a 1 HLA-DR and 2 HLA-B mismatch.

Table 3. Karpinski score and graft function.

Outcome	K score 0–4	K score 5–8	P value
1 year eGFR (n = 399)*	51 (37–66)	35 (26–52)	<0.001
3 year eGFR (n = 310)†	52 (34–64)	35 (24–52)	<0.001
5 year eGFR (n = 193)‡	46 (29–61)	36 (5–50)	0.06

Data expressed as median (IQR). Estimated glomerular filtration rate (eGFR) expressed as ml/min/1.73 m^2.

*Death before 1 year (n = 5), missing data (n = 4).

†3-year follow-up not yet reached (n = 62), death before 3 years (n = 16), missing data (n = 20).

‡5-year follow-up not yet reached (n = 179), death before 5 years (n = 24), missing data (n = 12).

likely that the use of PIKBs would lead to higher numbers of transplants from kidneys with scores 0–4 being performed, which would make the poorer outcomes in kidneys scoring more than four hard to explain in their analysis. Most studies have used wedge biopsies [11,18], as these are thought to confer a lower risk of postoperative bleeding. Our analysis used core biopsies, which are thought to better sample deep vessels and may avoid the over-representation of sclerosed subcapsular glomeruli [22–24]. However, even the vascular component score was not associated with graft outcome in our series. Sectioning and staining techniques were similar between the two UK groups (personal communication, Dr V. Bardsley, Cambridge, May 2018).

Table 4. Univariate linear regression analyses of estimated glomerular filtration rate (eGFR) at 1 year post-transplant.

Variable	One year post-transplant eGFR (n = 399)		
	Coefficient	95% CI	*P* value
K score	−4.06	−5.23 to −2.88	<0.001
Donor age	−0.65	−0.78 to −0.52	<0.001
Donor gender			
Male	Reference	–	–
Female	−5.54	−9.74 to −1.34	0.01
Donor type			
Donation after brain death	Reference	–	–
Donation after circulatory death	0.35	−4.18 to 4.88	0.88
Donor cause of death			
Stroke	Reference	–	–
Other	4.24	1.48 to 7.01	0.003
United Kingdom Kidney Donor Risk Index (UKKDRI)	−18.28	−23.59 to −12.95	<0.001
Recipient age	−0.07	−0.29 to 0.15	0.04
Recipient gender			
Male	Reference	–	–
Female	−1.96	−6.35 to 2.42	0.38
Recipient ethnicity			
Nonblack	Reference	–	–
Black	−0.76	−3.06 to 1.55	0.52
Recipient diabetes			
Nondiabetic	Reference	–	–
Diabetic	−0.32	−7.53 to 7.90	0.93
Graft number			
1	Reference	–	–
>1	−7.72	−13.88 to −1.57	0.01
HLA mismatch level*			
1	Reference	–	–
>1	−1.66	−7.86 to 4.54	0.60
Cold ischaemia time	0.01	−0.02 to 0.0	0.06

*Defined according to the UK allocation policy for deceased donor kidneys and was based on donor-recipient differences at HLA-A, HLA-B and HLA-DR loci: level 1 was a mismatch of 000; level 2 was a 0 HLA-DR and a 0/1 HLA-B mismatch; level 3 was a 0 HLA-DR and a 2 HLA-B mismatch, or a 1 HLA-DR and a 0/1 HLA-B mismatch; and level 4 was a 2 HLA-DR or a 1 HLA-DR and 2 HLA-B mismatch.

We acknowledge the weaknesses of our study. Firstly, a significant proportion of kidneys were not biopsied (23%), and of those that were biopsied, 30% did not contain sufficient glomeruli for scoring using Karpinski's criteria. However, there was no difference in baseline characteristics between those with an adequate biopsy and those with no/inadequate biopsy, indicating that there was no demonstrable selection bias in this study. Adequacy rates could have been improved by using a punch biopsy technique [22,25]. Secondly, the retrospective utilization analysis could only take account of those organs accepted for implantation at our unit; it is possible that access to a 'round-the-clock' emergency histopathology service might have encouraged clinicians to accept more marginal offers. Thirdly, a single histological scoring system was used, and it is possible that using different scoring systems may have led to different results. Fourthly, pathology slides were not re-read by a single histopathologist; it is possible that interpathologist interpretations [26], even amongst specialist renal pathologists [24,27], may vary sufficiently to mask an association between chronic changes and graft outcome. However, multiple histopathologists would be necessary to provide a 'round-the-clock' PIKB service, and therefore our analysis is pragmatic. Finally, the size of the study and/or the length of follow-up may have been insufficient to detect an association that might be present.

Interestingly, there was a significant association between K score and eGFR in our study. Given that

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Table 5. Multivariable linear regression analyses of estimated glomerular filtration rate (eGFR) at 1 year post-transplant.

	One year post-transplant eGFR (n = 399)		
Variable*	Coefficient	95% CI	P value
K score	−2.80	−4.17 to −1.43	<0.001
Donor gender			
Male	Reference	–	–
Female	−3.19	−7.32 to 0.94	0.13
Donor cause of death			
Stroke	Reference	–	–
Other	0.41	−2.42 to 3.24	0.77
United Kingdom Kidney Donor Risk Index (UKKDRI)	−13.02	−19.28 to −6.74	<0.001
Recipient age	−0.05	−0.22 to 0.12	0.61
Cold ischaemia time	−0.01	−0.02 to 0.00	0.03
Graft number			
1	Reference	–	–
>1	−10.19	−16.08 to −4.31	0.001

*Donor age was removed from these analyses due to multicollinearity with UKKDRI.

lower eGFR at 1-year post-transplant is correlated with inferior long-term graft survival [28–30], and that our study found a higher rate of PNF in kidneys with K scores of 5–8, it is possible that a larger sample size might have shown that K score predicted graft survival. However, if a larger study than ours is needed to detect a statistically significant association with graft survival, the predictive value of the Karpinski score for an individual organ is likely to be weak. Our analysis would suggest that the use of empirically designed histological scoring systems and rigid scoring thresholds to determine organ utilization seems overly simplistic [31]. If chronic donor histological changes are associated with graft survival, histological scoring systems need to be developed using appropriate statistical techniques, similar to those used to develop donor risk indices based on clinical factors [8,9]. This will require a significant dataset from multiple centres and may lead to combined clinicopathological scoring systems [32,33].

In order for clinicians to make deceased donor kidney utilization decisions on the basis of chronic donor histological changes, a tool with high predictive value for graft

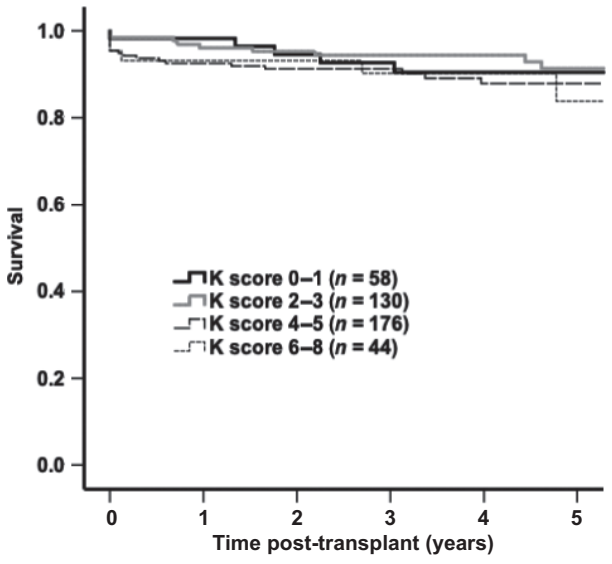

Figure 4 Karpinski (K) score and death-censored graft survival in single kidney-only transplants from deceased donors (n = 408).

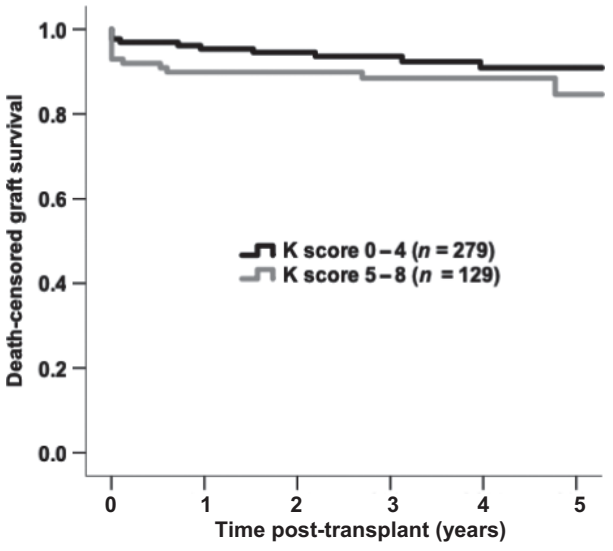

Figure 5 Karpinski (K) score and death-censored graft survival K score 0–4 (n = 279) versus K score 5–8 (n = 129).

Table 6. Univariate variable Cox regression analysis of death-censored graft survival (n = 408).

Variable	Hazard ratio	95% CI	*P* value
Karpinski score	1.1	0.94–1.33	0.20
Donor age	1.04	1.00–1.04	0.12
Donor gender			
Male	Reference	–	–
Female	1.12	0.60–2.10	0.71
Donor cause of death			
Stroke	Reference	–	–
Trauma	1.19	0.57–2.49	0.65
Other	1.58	0.57–4.39	0.38
United Kingdom Kidney Donor Risk Index (UKKDRI)	0.57	0.30–1.01	0.09
Recipient age	1.00	0.97–1.02	0.72
Recipient gender			
Male	Reference	–	–
Female	1.03	0.53–1.96	0.93
Recipient ethnicity			
Nonblack	Reference	–	–
Black	1.34	0.70–2.60	0.38
Recipient diabetes status			
Nondiabetic	Reference	–	–
Diabetic	1.10	0.39–2.05	0.88
Graft number			
1	Reference	–	–
>1	3.00	1.50–5.95	0.002
Donor type			
Donation after brain death	Reference	–	–
Donation after circulatory death	1.01	0.51–1.99	0.99
Cold ischaemia time	1.00	1.00–1.00	0.17
HLA mismatch level†			
1	Reference	–	–
>1	0.94	0.39–2.25	0.89

†Defined according to the UK allocation policy for deceased donor kidneys and was based on donor-recipient differences at HLA-A, HLA-B and HLA-DR loci: level 1 was a mismatch of 000; level 2 was a 0 HLA-DR and a 0/1 HLA-B mismatch; level 3 was a 0 HLA-DR and a 2 HLA-B mismatch, or a 1 HLA-DR and a 0/1 HLA-B mismatch; and level 4 was a 2 HLA-DR or a 1 HLA-DR and 2 HLA-B mismatch.

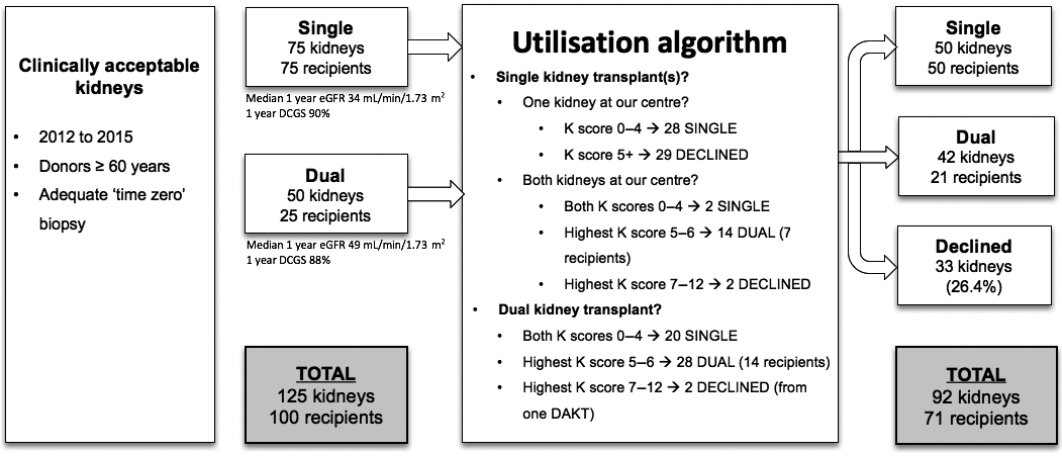

Figure 6 Organ utilization analysis. In those kidneys transplanted from deceased donors aged ≥60 years with adequate time-zero biopsies, Karpinski (K) scores were retrospectively analysed to determine utilization decisions if previously reported thresholds had been used.

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survival will be needed in order for it to be confidently applied to individual organs. Our study suggests that, at present, there is insufficient evidence to support the systematic use of the Karpinski score to decide whether or not to implant a deceased donor kidney.

Authorship

BP: collected local data, carried out the statistical analysis and contributed to the writing of the manuscript. TK: contributed to the statistical analysis and the writing of the manuscript. KA, HA and NK: contributed to local data collection and the writing of the manuscript. RH: co-initiated the project, and contributed to the writing of the manuscript. NS and CH: provided the histopathological data and contributed to the writing of the manuscript. CC: co-initiated the project, was the senior author and participated in local data collection, statistical analysis and the writing of the manuscript.

Funding

The authors have declared no funding.

Conflict of Interest

The authors have declared no conflicts of interest.

Acknowledgements

The authors gratefully acknowledge the contributions of other consultant surgeons in the department (Mr Geoff Koffman, Mr John Taylor, Mr Francis Calder, Professor Nizam Mamode, Mr Jonathon Olsburgh, Mr Martin Drage, Mr Ioannis Loukopoulos and Mr Nikolaos Karydis), and the renal histopathologists who reported the kidney biopsies (Dr Patrick O'Donnell, Dr Fahim Tungekar, Dr Robert Hangartner and Dr Ranmith Perera). We also thank Dr Patrick Trotter, NHS Blood and Transplant, who provided UKKDRI data.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Box and whisker plot of Karpinski (K) score and graft function at (A) one- (n = 399), (B) three- (n = 310), and (C) 5-years (n = 193) post-transplantation.

Figure S2. Karpinski score components and death-censored graft survival (DCGS) in single kidney-only transplants from deceased donors (n = 408).

Figure S3. Subgroup analyses of Karpinski (K) score and DCGS in higher risk deceased donor groups.

Figure S4. Actual death-censored graft survival of single and double adult kidney transplants (DAKT) from deceased donors aged ≥ 60 years, versus application of a retrospective organ utilization algorithm based on Karpinski scores.

Table S1. Donor and recipient selection criteria for dual adult kidney transplantation.

Table S2. Donor and recipient characteristics included in the organ utilization analysis.

Table S3. Actual 1-year eGFR in single and dual adult kidney transplants (DAKT) versus outcomes with retrospective application of an organ utilization algorithm based on Karpinski scores.

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