Is the Kidney Donor Risk Index a step forward in the assessment of deceased donor kidney quality?

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ABSTRACT

The allocation of deceased donor kidneys has become more complex because of the increasing spectrum of donors and recipients age and comorbidities. Several scoring systems have been proposed to evaluate the donor quality of deceased donor kidneys, based on clinical, pathological or combined parameters to predict the risk of renal allograft failure. Nonetheless, besides the dichotomous extended criteria donor (ECD) score, none of the others have been used in clinical practice because of numerous reasons, ranging from lack of robust validation to the technical challenges associated with the evaluation of donor biopsies. Recently, the Kidney Donor Risk Index (KDRI) and Profile Index (KDPI) were introduced in the USA as a refined version of the ECD score. This scoring system is based on 10 donor factors, therefore providing a finely granulated evaluation of donor quality without the need of a kidney biopsy.

Here, we review the advantages and drawbacks of the main scoring systems, and we describe the components of the KDRI and KDPI. It is an easily accessible online tool, based solely on donor factors readily available at the moment of the donor offer. Importantly, the KDPI has also been made part of the ‘longevity matching’ allocation in the USA, where the best kidneys are allocated to the recipients with the longest predicted post-transplant survival. The KDRI should provide us with a robust qualitative evaluation of deceased donor quality, and therefore will probably play a role in deceased donor kidney allocation policies across Europe in the near future.

Keywords: deceased donors, donor biopsy, Kidney Donor Risk Index (KDRI), marginal donors, scoring system

INTRODUCTION

Nowadays, to increase the deceased donor organ pool, transplant centres use kidneys from ‘marginal’ donors including older donors. This led to the dilemma for clinicians of whether to accept an older kidney associated with lower allograft survival or to let the patient remain on dialysis knowing the mortality risk while waiting for the next offer. To guide
clinicians in their choice to accept such 'marginal' kidneys but with still sufficient quality to be beneficial for the recipients, several scoring systems have been developed. They include characteristics of the donor with or without characteristics of the recipient, with the aim to predict the risk of graft failure.

**ASSESSING KIDNEY DONOR QUALITY**

The first parameter that was found to negatively impact graft survival was a higher donor age. For instance, an analysis in the early 1990s of 31 000 recipients showed that 3-year graft survival was 78% with donors aged between 20 and 24 years, while kidneys from donors >60 years had a survival of only 58% [1]. Similar results were reported by numerous other investigators [2]. This was not unexpected since the aging kidney loses nephrons and shows a stepwise reduction in GFR [3]. However, the evaluation of old donors should be made with caution for two reasons. First, a normal creatinine often underestimates kidney function because of a reduced muscle mass. Second, the decline in renal function with age is very heterogeneous [3]. Therefore, a significant minority of co-morbidity-free older donors provides qualitative good kidneys.

Next to age, donor co-morbidities such as established hypertension and death from cerebrovascular accident are also surrogate markers of lower kidney function and are predictors of reduced graft survival. To incorporate these parameters as a guide in the decision-making, the concept of ECD was introduced in 2002 [4]. ECD were defined as those whose relative risk of allograft failure was >1.7 when compared with a standard donor. They included all donors aged ≥60 years, or those aged between 50 and 59 years who meet at least two of the following criteria: serum creatinine >1.5 mg/dL, a cerebrovascular accident as the cause of death or a history of hypertension. These three criteria, together with age, were considered as surrogate markers of a reduced nephron mass. There are important limitations to this score. First, donor age >60 years is sufficient to be qualified as 'ECD', although as stated above, the decline in kidney function with age is a heterogeneous process. Second, there is an incremental risk of allograft failure when a donor combines the four risk factors, therefore allowing a more detailed assessment of donor quality, with adjusted hazard ratios rising from 1.7 up to 2.69. This important information, able to provide further evaluation of donor kidney quality, is however not taken into account and the donor is simply reported as 'Standard Criteria Donor (SCD)' or 'ECD'. Finally, the binary SCD/ECD classification system is known to misclassify kidneys in both directions: some kidneys labelled as SCD have a reduced allograft survival, while some ECD kidneys perform well.

It therefore became clear that fine-tuning of the dichotomic ECD/SCD criteria was needed to give a more precise and graded evaluation of the donor kidney quality. Several prognostic scoring systems were developed that included more donor variables—either clinical or histological—and also some including recipient parameters to predict allograft failure [5].

Nyberg studied 34 324 patients reported to the UNOS Scientific Renal Transplant Registry (SRTR) between 1994 and 1999 who received deceased adult donor kidneys [6, 7]. A scoring system was developed from five variables: donor age, history of hypertension, creatinine clearance, cause of death and the number of HLA-mismatches. A higher score (0–39) and grade (A–D) reflected poorer organ quality. ‘Marginal’ kidney donors were those with a score above 20, and included all previously defined ECD. Schold et al. [8], using the SRTR database, added donor/recipient CMV serology, donor ethnicity, history of diabetes and cold ischaemia to calculate the ‘donor risk grade’ (from 1 to IV). This score was claimed to better predict graft survival than the previous ones. The Nyberg and Schold scores were, however, not replicated in independent cohorts and are not widely used in daily practice.

Besides clinical parameters, the value of donor biopsy findings is hotly debated as an independent predictor of donor quality above and beyond clinical indices. In 1995 the use of routine pre-transplant biopsies was advocated for older donors (>50 years) and those with non-traumatic cerebrovascular accidents [9]. In a retrospective analysis of 65 baseline biopsies, a percentage of >20% glomerulosclerosis was associated with an increased incidence of delayed graft function and poor outcome of transplanted kidneys. These data were re-examined by Edwards et al. [10] who established, in a cohort of 3444 deceased donor kidneys, that calculated donor creatinine clearance does, and percentage glomerulosclerosis on donor kidney biopsies does not, correlate well with 1-year graft survival and function. Along the same line, a prospective study of 200 donors who underwent a wedge biopsy found that the proportion of glomerulosclerosis correlated with graft function in the simple regression analysis, but not when donor age was taken into account [11]. Sung analysed 12 536 recovered ECD kidneys, 75% of which were biopsied. While there was no association between the percentage of glomerulosclerosis in these ECD kidneys and graft outcomes, the rates of discard increased stepwise as the proportion of glomerulosclerosis increased above 10% [12]. Therefore, in the absence of large studies, the percentage of glomerulosclerosis alone should not be used as the sole criterion for discarding recovered deceased donor kidneys [10, 12]. Others have reported that the results of more extensive analysis of donor biopsy, including interstitial and tubular, but also, importantly, vascular components, impact on graft outcome. These reports must, however, be analysed with caution. Karpinski studied pre-transplant biopsies from 34 donors. Donor renal pathology was scored 0–3 (none to severe disease) in four areas: glomerulosclerosis, interstitial fibrosis, tubular atrophy and vascular disease [13]. This score was later used by the Remuzzi group [14]. A donor vessel score of 3/3 was associated with a 100% incidence of delayed graft function and a worse recipient creatinine at 1 year. Along the same line, Bosmans reported that, among 50 consecutive adult recipients of a cadaveric allograft, fibrous intimal thickening at implantation was the main determinant of the functional and morphologic outcome at 1.5 years [15]. More recently, the impact of moderate arteriosclerosis and/or arteriolosclerosis in the donor was found to be a significant predictor of graft outcome in both SCD and ECD in a series of 597 kidney transplant recipients [16]. These studies suffer from the following drawbacks: inhomogeneous definition of vascular lesions, impairing the ability to perform between-

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study comparisons, low numbers of patients and lack of validation in independent cohorts. Furthermore, multi-variate analysis that includes donor age and function expressed as continuous variables is lacking, thereby allowing biopsy findings to represent the only parameter of graft quality. Therefore, they erroneously appear as independent predictors of allograft failure. Remuzzi and his group reported that the realization of the Karpinski score on pre-transplant donor histology was instrumental in optimizing the outcome of grafts from donors >60 years. However, in our view, a low number of patients, and again a lack of clear evidence showing independence from clinical donor factors in multi-variate analysis, limit the generalizability of these findings [14]. The Maryland Aggregate Pathology Index (MAPI) included glomerular, tubular, interstitial and vascular indices to build a pathology score that was shown to predict graft failure. A retrospective design, the lack of assessment of feasibility of the sophisticated pathological morphometric analysis, and the lack of confirmatory studies [17] again limit the widespread use of this score today.

More recently, the results of donor biopsies were associated with donor characteristics in an attempt to develop clinico-pathological scores of better predictive ability, the two largest studies reporting on 191 [18] and 542 patients [19]. Anglicheau, in a retrospective series of 191 donor/recipient pairs, found that associating donor glomerulosclerosis together with donor creatinine and history of hypertension did improve the predictive ability for low estimated creatinine clearance at 1 year [18]. Of note, however, donor age was not predictive of low estimated creatinine clearance at 1 year, at odds with many reports. Addition of donor glomerulosclerosis also led to only a marginal improvement in the concordance statistic over the clinical score alone (from 0.78 to 0.84). The concordance statistic (C) estimates the probability of concordance between predicted and observed responses: a value of 0.50 indicates zero predictive ability whereas a value of 1.0 indicates perfect prediction. After studying retrospectively >500 donor/recipients pairs, the Leuven group designed another score that involves donor age and donor biopsy characteristics, leading to a concordance statistic of 0.81 for 5-year allograft loss [19]. Importantly, however, donor renal function was not taken into account for this analysis.

Therefore, while donor biopsy findings do have a predictive ability, it remains unclear to what extent they would improve a score where donor age and function would have been integrated as continuous variables. Furthermore, we must be aware of several pitfalls of the evaluation of the donor kidney biopsies [20]. For instance, frozen sections are not appropriate for detailed morphometric analysis; the reliability of the glomerular score depends on the number of glomeruli; wedge biopsies can overestimate glomerulosclerosis; formalin fixation will add several hours to cold ischaemia time. Inter-observer variability is also a serious issue, even more so when inexperienced pathologists on call score the biopsy. And finally, donor biopsy findings have not been shown to be an independent predictor of allograft survival beyond readily accessible donor data. A new index that allows a ‘clinician-friendly’ and refined appreciation of donor quality, without requiring donor histology, was welcome.

**The Kidney Donor Risk Index (KDRI)**

In an attempt to improve on previous models and to provide a more continuous granulated risk score, Rao et al. [21] developed the Kidney Donor Risk Index (KDRI). This model avoids categorization and is based on the association between 10 donor characteristics and graft survival. It was established in 69 440 adult, ABO-compatible, solitary, first-time deceased donor kidney recipients in the USA from 1995 to 2005 by a multivariable Cox proportional hazards regression model linking donor data with graft outcomes. The factors are age, height, weight, ethnicity, history of hypertension or diabetes, cause of death, serum creatinine, hepatitis C serology (HCV) and donation after cardiac death (DCD). The 10 different factors are surrogates of donor quality and nephron mass. Age has the highest impact on KDRI, and even more so when age is >50 years. Each additional year was associated with a significant 1% additional risk of graft failure. The KDRI also rises when the donor is younger than 18 years. Concerning height, the KDRI decreases as the donor is taller. Weight adds to the KDRI but only when it is lower than 80 kg. The meaning is that a lower height and weight are surrogate markers for a reduced renal mass, all other parameters being equal. The KDRI also increases in cases of African American donors, the presence of diabetes and hypertension, a positive HCV serology, donation after cardiac death (DCD), and a cerebrovascular accident as the cause of death. The KDRI rises in parallel with creatinine, but the increase becomes less steep when serum creatinine is >1.5 mg/dL. Factors like cigarette use and donor gender have been examined but were not statistically significant in their association with graft loss.

Of note, several factors pertaining to the recipient and/or transplant procedure (cold ischaemic time, degree of HLA mismatching, single versus double versus en-bloc kidneys) can also be used to calculate a ‘full’ KDRI [21]. Since these factors are generally not known at the time when offers are made, and are candidate-specific, the donor-only KDRI is the version that was implemented. In addition, virtually no predictive ability is lost with the ‘donor factors only’ version. Indeed, it has a concordance statistic of 0.6 compared with the full KDRI version which has a concordance statistic of 0.601 [22]. Until recently, the reference donor (KDRI = 1.00) was defined as a 40-year-old non-African American male, height 1.70 m, weight 80 kg, with a serum creatinine of 1.0 mg/dL, without diabetes, hypertension or a cerebrovascular cause of death, who is HCV negative and brain dead. More recently, a KDRI of 1 is that of the median (50th percentile) donor of the prior calendar year. The KDRI is an estimate of the relative risk of post-transplant kidney graft failure from a particular deceased donor compared with the median donor. For example, a donor with a KDRI of 1.28 confers an estimated risk of graft failure that is 1.28 times that of the median donor. The KDRI generally ranges from 0.5 to 3.5: higher values are associated with a lower expected graft survival and vice versa. There is a stepwise decrease in graft survival with each KDRI quintile, with the lowest (0.45 < 0.79) being associated with a graft half-life of 13.6 years, and the highest (>1.45) of 7.5 years.
Importantly, the predictive power of the KDRI is highest at the two extreme categories ($C = 0.78$) and lowest for donors in the middle range ($C = 0.58$) [21]. Based on this KDRI, the Kidney Donor Profile Index (KDPI) was determined: a numerical map to express the quality of the donor kidneys relative to other kidneys (http://optn.transplant.hrsa.gov/). For example, a donor with a KDPI of 90% has a KDRI greater than 90% of donors in the chosen reference population. Lower KDPI values are associated with increased donor quality and vice versa.

### KDRI and KDPI: Are They Validated? What Are Their Purposes?

First of all, the KDRI/KDPI is an easily applicable scoring system that provides a uniform platform to initiate and to compare clinical studies. Indeed, the donor data needed to calculate the KDRI are readily available from most of the European donor procurement organizations, such as Eurotransplant, at the time of the donor offer. The KDRI/KDPI calculator is freely accessible on the web (http://optn.transplant.hrsa.gov/).

<table>
<thead>
<tr>
<th>Donor factors</th>
<th>Donor A</th>
<th>Donor B</th>
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<td>Cardiovascular accident as cause of death</td>
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</tr>
<tr>
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<td>ECD/SCD</td>
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Table 1. Re-classification of ECD and SCD with the KDRI

This table highlights the large variability in the donor quality of ECDs and SCDs with as example, an SCD with a high KDRI (lower estimated quality), compared with an ECD with a lower KDRI (higher estimated quality). KDRI, Kidney Donor Risk Index; KDPI, Kidney Donor Profile Index; ECD, extended criteria donor; SCD, standard criteria donor.
resources/allocationcalculators.asp?index=81) allowing its calculation for each donor offer (Figure 2).

Second, as a result, transplant programmes may define thresholds of KDRI/KDPI they find acceptable or not for each of their individual recipients on the waiting list, knowing that it should provide a better prediction of graft outcomes than the SCD/ECD score. Several groups have already evaluated the predictive ability of the KDRI to assess graft outcomes. Thus, Pine observed among 184 recipients of DCD kidneys that both patient and graft survival was significantly lower at 5 years when the KDRI was higher than 1.5 [24]. More recently, the group of Tullius reported, using KDPI as index of donor quality, that elderly recipients (>70 years) gained no relative benefit from medium-quality kidneys over low-quality kidneys [25]. According to a Korean group, the KDRI has a greater predictive ability regarding creatinine clearance and graft survival among transplants with a short cold ischaemic time, than the SCD/ECD score or donor pathology [26].

Third, a new allocation policy based on the KDPI will be implemented by the United Network of Organ Sharing in the USA by the end of 2014 (http://optn.transplant.hrsa.gov/). Each candidate on the waiting list will have his ‘estimated post-transplant survival score (EPTS)’ calculated to participate in ‘longevity matching’ allocation. The EPTS is based on four different factors: candidate time of dialysis, current diagnosis of diabetes, prior solid organ transplants and candidate age. The 8-year post-transplantation survival is 90% for those 20% of recipients with the highest EPTS. At the opposite, survival is lower than 50% at 8-year for the 20% of candidates with the lowest EPTS (http://optn.transplant.hrsa.gov/ContentDocuments/Guide_to_Calculating_Interpreting_EPTS.pdf). The purpose is to match the longevity of the donor kidney with the estimated post-transplant survival in order to maximize the number of life years lived with the 20% best recovered organs, while minimizing life years lost following death with a functioning graft. Candidates with EPTS ≤20% will receive priority for kidneys from donors with KDPI ≤20%, before other candidates at the local, regional and national levels. The mean estimated graft half-life of kidneys with KDPI <20% is 11 years, approximating the 12 years observed with living donor kidneys. At the other end of the spectrum, kidneys with KDPI between 86 and 100% have a mean estimated graft half-life of 5.6 years. Anyway, the EPTS score is not used in allocation of kidneys from donors with KDPI scores greater than 20%. This policy somehow mirrors the ‘old-for-old’ allocation scheme from Eurotransplant, where kidneys from donors >65 years are offered first to recipients >65 years, in order to maximize the use and utility of ECD kidneys.

Finally, there might be a reluctance to transplant kidneys with the highest KDPI (>80%). Indeed, among organs retrieved between 2002 and 2012, 36 and 63% of kidneys with KDPI between 80–90% and >90% respectively, were discarded in the USA [27]. To tackle this issue, the performance of a pre-implantation biopsy evaluated according to the Karpinski-Pirani-Remuzzi score has been shown to help to allocate these kidneys either as single or dual kidney transplantation [28]. While dual kidney transplantation has not gained popularity worldwide due to increased surgical time and complications, this biopsy-based allocation of marginal grafts allowed for a limited discard rate of 15% for kidneys with KDPI of 80–90% and 37% for kidneys with a KDPI of 91–100% [28].

CONCLUSION

In this time of organ shortage, a thoughtful allocation of donor kidneys is needed. The KDRI provides the clinician with a guide to objectively assess the quality of the increasing number of ‘marginal’ donors. However, we need to realize that the KDRI does not account for any recipient or donor/recipient parameters.

The KDRI is an easily applicable scoring system which provides a uniform platform to initiate and to compare clinical studies. We expect more studies to be published in the near future.
future, to further validate this scoring system in several populations. In Europe, this might be an opportunity to acquire a standardized uniform policy to meet the growing demand of donor kidneys and to maximize the use of both the best kidneys as well as those from ‘marginal’ donors.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. We also declare that the results presented in this paper have not been published previously in whole or part.

REFERENCES


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