Clinical Kidney Journal

ckj

OXFORD

era edta
LEADING EUROPEAN NEPHROLOGY

Clinical Kidney Journal, 2019, vol. 12, no. 4, 569–573

doi: 10.1093/ckj/sfy130
Advance Access Publication Date: 8 January 2019
Original Article

ORIGINAL ARTICLE

Assessing the discrimination of the Kidney Donor Risk Index/Kidney Donor Profile Index scores for allograft failure and estimated glomerular filtration rate in Ireland's National Kidney Transplant Programme

Donal J. Sexton[1], Patrick O'Kelly[1], Claire Kennedy[1], Mark Denton[1], Declan G. de Freitas[1,2], Colm Magee[1], Conall M. O'Seaghdha[1,2] and Peter J. Conlon[1,2]

[1]Department of Nephrology and Kidney Transplantation, National Kidney Transplant Service, Beaumont Hospital, Dublin, Ireland and [2]Royal College of Surgeons in Ireland, Dublin, Ireland

Correspondence and offprint requests to: Donal J. Sexton; E-mail: donalsexton2@beaumont.ie

ABSTRACT

Background. The Kidney Donor Risk Index (KDRI)/Kidney Donor Profile Index (KDPI) is relied upon for donor organ allocation in the USA, based on its association with graft failure in time-to-event models. However, the KDRI/KDPI has not been extensively evaluated in terms of predictive metrics for graft failure and allograft estimated glomerular filtration rate (eGFR) outside of the USA.

Methods. We performed a retrospective analysis of outcomes in the Irish National Kidney Transplant Service Registry for the years 2006–13. Associations of the KDRI/KDPI score with eGFR at various time points over the follow-up and ultimate graft failure were modelled.

Results. A total of 772 patients had complete data regarding KDRI/KDPI calculation and 148 of these allografts failed over the follow-up. The median and 25–75th centile for KDRI/KDPI was 51 (26–75). On repeated-measures analysis with linear mixed effects models, the KDRI/KDPI (fixed effect covariate) associated with eGFR over 5 years: eGFR = −0.25 (standard error 0.02; $P < 0.001$). The variability in eGFR mathematically accounted for by the KDRI/KDPI score was only 21%. The KDRI/KDPI score did not add significantly to graft failure prediction above donor age alone (categorized as > and <50 years of age) when assessed by the categorical net reclassification index.

Conclusions. In this cohort, while the KDRI/KDPI was predictive of eGFR over the follow-up, it did not provide additive discrimination above donor age alone in terms of graft failure prediction. Therefore it is unlikely to help inform decisions regarding kidney organ allocation in Ireland.

Keywords: epidemiology, ESRD, graft failure, immunosuppression, kidney transplantation

Received: 21.9.2018. Editorial decision: 27.11.2018

INTRODUCTION

The Kidney Donor Risk Index (KDRI)/Kidney Donor Profile Index (KDPI), derived from donor characteristics, was developed in the USA in an effort to devise an objective means of assessing donor organ suitability based on predicted graft survival [1]. The association of the KDRI with graft failure is founded on Cox proportional hazards models of 70 000 donors in the USA from 1995 to 2005 [2], and use of this score has influenced kidney organ allocation in the USA [3, 4]. Although the KDRI/KDPI score is associated with graft failure, it has not been evaluated extensively in terms of prediction metrics for kidney transplant outcomes outside the USA, where KDRI profiles and distributions may differ [5]. Recently, other investigators have attempted to assess the scoring system in European cohorts in comparison with the USA. This single-centre study found an association between the KDPI score and graft failure; however, the absolute risk of graft failure was higher in the USA [6].

High KDRI/KDPI donor kidneys may be considered by some to be unsuitable for transplantation and discarded [4, 7], yet many of these kidneys may not be destined to fail solely on the basis of the donor factors as summarized by the KDRI/KDPI score [4, 8]. Another recent single-centre study assessing the KDRI/KDPI score in a European cohort found favourable outcomes in kidney organs with a high KDPI score [9]. This points towards variable discrimination and calibration in cohorts dissimilar from the validation cohort. We examined whether the KDRI/KDPI provides additive discrimination for graft failure beyond donor age in isolation in the Irish National Kidney Transplant Programme. Lastly, since estimated glomerular filtration rate (eGFR) is the most common assessment of allograft function in clinical practice, we considered whether the KDRI/KDPI predicts eGFR over long-term follow-up.

MATERIALS AND METHODS

This was a retrospective analysis of the Irish National Renal Transplant database to assess eGFR and graft outcomes over long-term follow-up in deceased donor kidney transplants for the years 2006–13. Component variables of the KDRI score include age, height, weight, ethnicity/race and history of hypertension or diabetes, serum creatinine, hepatitis C virus status, cause of donor death and whether the donor met criteria for circulatory death. Complete variables necessary to calculate the composite KDRI/KDPI/KDRI were available for a subset of this database ($N = 772$).

We examined associations of the KDRI/KDPI/KDRI score with graft failure and eGFR at various time points over the follow-up. These associations were assessed using linear regression, time-to-event models and repeated-measures linear mixed effects models, respectively.

We used generalized linear mixed effects models, allowing intercept, slope and time to vary randomly to investigate the within- and between-subject variation in eGFR on repeated testing considering KDRI/KDPI as a fixed effect. Metrics of predictive performance of the KDRI/KDPI for allograft failure were assessed separately with net reclassification indices (NRIs) based on two different thresholds of the KDRI/KDPI score (with KDRI/KDPI as a categorical variable) [10, 11]; ≥35 and ≥85 compared with donor age as a reference (< or >50 years). Donor age was divided into age > and <50 years. We chose ≥85 as an established high-risk threshold [7, 12]. R statistical software (R Project for Statistical Computing, Vienna, Austria), STATA version 13.1 (StataCorp, College Station, TX, USA) and SAS University Edition (SAS Institute, Cary, NC, USA) were used for data analysis and graph creation. Figure 1 was generated using SAS University Edition. eGFR was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation. In Ireland, all donors included in the analysis were hepatitis C negative. Research ethics committee approval was obtained for this study and all research methodology complied with the Declaration of Helsinki.

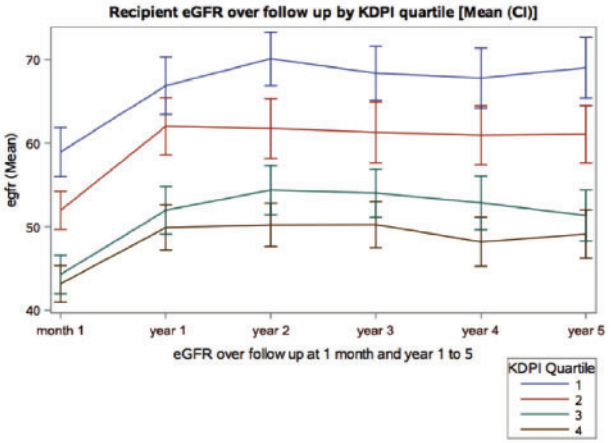

FIGURE 1: eGFR over 5 years follow-up by quartile of the KDRI/KDPI score in deceased donor renal transplants ($N = 772$).

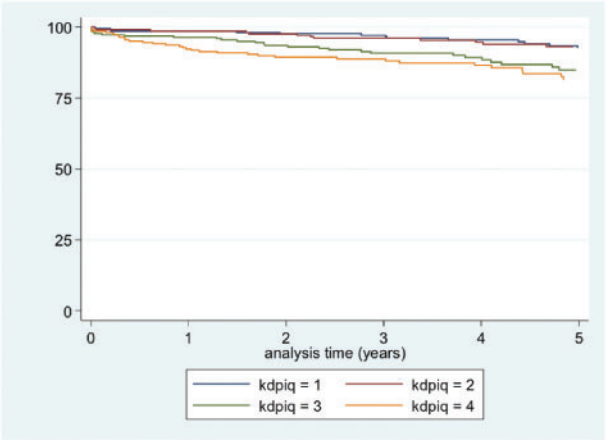

FIGURE 2: Death-censored graft survival by KDRI/KDPI score quartile in deceased donor transplants in Ireland.

RESULTS

The median and 25–75th centile of the KDRI/KDPI was 51 (26–75) and that of the KDRI was 1.10 (0.90–1.3). Death censored time to graft failure was associated with the KDRI/KDPI score (Figure 2 and Table 1).

KDRI/KDPI association with eGFR cross-sectionally at each time point

The KDPI/KDRI had a negative linear relationship with eGFR when assessed cross-sectionally at each single time point of the follow-up.

Table 1. Allograft survival and deceased donor characteristics by KDRI/KDPI quartile

Graft survival by quartile of KDRI/KDPI and KDRI scores scaled to the median.					
		Kidney graft survival			
KDRI/KDPI	KDRI	1 year (%)	2 years (%)	3 years (%)	5 years (%)
1–25%	0.591–0.825	98.64	97.69	97.14	92.55
26–50%	0.825–1.00	98.63	97.65	96.02	93.07
51–75%	1.003–1.182	96.35	93.47	90.77	84.91
76–100%	1.183–1.962	92.24	89.31	88.72	81.39

Patient characteristics				
Donor characteristics	KDRI/KDPI Q1, *n* (%)	KDRI/KDPI Q2, *n* (%)	KDRI/KDPI Q3, *n* (%)	KDRI/KDPI Q4, *n* (%)	P-value
Age <18 years	24 (11)	11 (5)	0 (0)	0 (0)	<0.001
18–50 years	196 (89)	196 (90)	104 (47)	22 (10)	
>50 years	0 (0)	12 (5)	115 (53)	197 (90)	
Height <170 cm	42 (19)	81 (37)	96 (44)	139 (63)	<0.001
Weight <80 kg	115 (52)	132 (60)	120 (55)	142 (65)	0.036
History of hypertension	1 (.5)	9 (4)	44 (20)	89 (41)	<0.001
History of diabetes	0 (0)	6 (3)	2 (1)	23 (11)	<0.001
Cause of death (cerebrovascular accident)	2 (1)	7 (3)	7 (3)	23 (11)	<0.001
Serum creatinine >1.5 mg/dL	9 (4)	6 (3)	14 (6)	22 (10)	0.007
Hepatitis C virus status					
Donation after circulatory death status	0 (0)	4 (2)	5 (2)	5 (2)	0.094

Table 2. Discrimination metrics for graft failure for two arbitrary thresholds of the KDRI/KDPI restricted to those with at least 5 years of follow-up [N = 701, of which 148 were graft failures (21%)]

Threshold	Accuracy (25th-75th centiles)	C statistic	Sensitivity	Specificity	PPV	NPV	Odds ratio (25th-75th centiles)
KDRI/KDPI ≥ 35	0.44 (0.40–0.48)	0.56	0.35	0.76	0.85	0.24	1.77 (1.17–2.69)
KDRI/KDPI ≥85	0.74 (0.71–0.78)	0.56	0.87	0.26	0.82	0.35	2.43 (1.56–3.78)

NPV, negative predictive value; PPV, positive predictive value.

Linear regression. The recipient age-adjusted KDRI (scaled) was associated (adjusted R^2) with an eGFR at 1 month (0.14), at 3 months (0.20), at 1 year (0.15), at 2 years (0.16), at 3 years (0.14), at 4 years (0.15) and 5 years (0.15), with all P-values <0.001.

eGFR by KDRI quartile at 1 and 5 years

At Year 1 post-transplant. eGFRs (25th-75th centiles) by quartile of the KDRI were 69.2 (57.6–82.5) mL/min/1.73m^2 ($n = 172$) in Quartile 1, 59.4 (50.2–74.5) ($n = 171$) in Quartile 2, 51.9 (42.2–62.2) ($n = 176$) in Quartile 3 and 48.3 (38.5–58.5) ($n = 162$) in Quartile 4 ($P < 0.001$ for comparisons).

At Year 5 post-transplant. eGFRs (25th-75th centiles) by quartile of the KDRI were 74.5 (60.5–88.2) mL/min/1.73 m^2 in Quartile 1 ($n = 110$), 64.6 (51.7–83.2) ($n = 104$) in Quartile 2, 48.8 (34.4–61.6) ($n = 85$) in Quartile 3 and 43.6 (37.5–58.1) ($n = 69$) in Quartile 4 ($P < 0.001$ for comparisons).

Linear mixed effects models

We modelled eGFR over seven repeated measurements at 1 month, 3 months and Years 1–5 post-transplant. The KDRI/KDPI (fixed effect covariate) associated inversely with eGFR >5 years of follow-up (see Figure 1): estimate −0.26 (standard error 0.02; $P < 0.001$). The variability in eGFR mathematically explained by the KDRI/KDPI alone was 23.4% after adjusting for recipient age (time-varying covariate).

Cross-tabulation (confusion) matrix

The predictive metrics associated with two arbitrary thresholds for KDRI/KDPI are displayed in Table 2. The accuracy for graft failure improves with higher KDRI/KDPI scores, although sensitivity increases with higher KDRI/KDPI thresholds, specificity decreases (see Table 2).

Categorical NRI

In this model, we consider a hypothetical scenario whereby graft failure as predicted by donor age alone is used as the reference for comparison of the predictive abilities of two thresholds of KDRI/KDPI, ≥35 and ≥85. The donor age category comprised of donor age > and <50 years was the reference comparison.

- The ≥35 KDRI/KDPI threshold versus donor age (≥50 years) at the cut-off risk thresholds of 0.1, 0.2, 0.3 and 0.4: NRI −0.06 [95% confidence interval (CI) −0.14–0.03), P for trend = 0.20.

- The ≥85 KDRI/KDPI threshold versus donor age (≥50 years) at the cut-off risk thresholds of 0.1, 0.2, 0.3 and 0.4: NRI 0.10 (95% CI −0.02–0.23), P for trend = 0.07.

Comparison of KDRI/KDPI with donor age alone in predicting outcomes

Graft survival (death-censored graft survival). In this cohort, KDRI was also associated with time to graft failure [hazard ratio (HR) 1.47 (95% CI 1.29–1.69), $P < 0.001$ per unit increase in KDRI (in quartiles)]. Harrell's C statistic measuring concordance of individual predicted HRs with outcome was 0.62 (moderate predictive result). For donor age alone (by quartile) [HR 1.47 (95% CI 1.28–1.68), $P < 0.001$], Harrell's C concordance was also 0.62 for the donor age quartile. There was no significant difference between the two Harrell's C statistics for KDRI quartile and donor age quartile for graft failure, suggesting that donor age alone may have similar performance to KDRI/KDPI score.

DISCUSSION

Although the KDRI/KDPI associated with graft failure in this study, a high KDRI/KDPI was not synonymous with graft failure, a finding also reported in other studies [13, 14]. In our cohort, the KDRI/KDPI did not appear to add significantly to discrimination for graft failure above donor age alone based on a cut-off of > or <50 years of age in an NRI-based analysis. As a result, the KDRI/KDPI is not likely to be reliable in isolation to predict graft failure or to decide on discarding donor organs in Ireland. This parallels our findings on histological features of pre-implant kidney biopsies [15].

A study from The Netherlands assessed the discrimination of KDRI for graft failure and also found it to be poor [16]. This study found that adding variables such as inotrope use prior to donation and an interaction term between circulatory death and prolonged cold ischaemia time improved this discrimination [16]. Other groups have assessed the predictive ability of the KDRI/KDPI and suggested poor performance in a paediatric population [17]. Another recent study assessing the KDRI/KDPI in a European cohort also found favourable outcomes in kidneys from donors with high KDRI/KDPI scores [9].

Clinical prediction models ought to be assessed on both discrimination and calibration [18]. Discrimination refers to the ability of the model to differentiate those at higher risk of the outcome from those who are not, whereas calibration is the ability of the model to estimate the absolute risk of the outcome, in this case graft failure [18]. Suboptimal external validity can result in models struggling to maintain calibration across diverse populations, since their ability to estimate the absolute risk of the outcome may vary across different populations.

To this end, KDRI/KDPI scores are known to vary across different transplant programmes. The median score in our sample was 1.10, which appears lower than that of the USA (1.24 in 2012) [16]. The absolute risk of graft failure, the outcome of interest in this study, is also known to vary across different transplant programmes and rates in Ireland are lower than in the USA. Discrimination for any predictive model may vary across cohorts, particularly if the constituent variables of the model also vary as they do across transplant programmes, such as donor hepatitis C status and the frequency of donors with circulatory death, among others factors.

The KDRI/KDPI may have positively affected some kidney transplant programmes. A study from Belgium looking at the implementation of the KDRI/KDPI score actually noticed an increase in transplant rates by 26% between 2015 and 2016 as a result of a lower discard rate [1]. Prior to implementation, the median KDRI at this centre was 0.85 and increased to 0.97 after KDRI/KDPI incorporation, suggesting an increased use of donor kidneys previously judged as inappropriate for use [1]. This highlights the fact that transplant programmes are heterogeneous in terms of both the KDRI/KDPI profile of donors and the absolute risk of graft failure. Therefore the performance of the KDRI/KDPI may be expected to vary across different programmes and thus calibration of the model may be difficult to maintain.

Our findings in relation to the association of the KDRI/KDPI score and eGFR align with those of Gandolfini *et al.* [19]. If the KDRI/KDPI can be considered a composite of all donor factors, then its association with graft failure in this retrospective cohort study would make it seem that non-donor factors may have been more influential. In addition, although the KDRI/KDPI as a composite of donor factors did associate with eGFR, perhaps non-donor factors predominated since the KDRI/KDPI accounted for only 21% of the eGFR variability over time in linear mixed effects models. These factors might include recipient factors, immunosuppression protocols as well as recipient compliance and which may be more amenable than donor factors to modification. Whether the KDRI/KDPI can be used to identify those recipients of deceased donor kidney transplants with an eGFR lower than expected by donor factors has not been evaluated.

Limitations of the study include its retrospective design. In addition, the protocols used in Ireland likely differ from those in the USA in terms of the typical immunological risk profile of recipients, which may result in lower graft failure in this context. In Ireland, efforts are made to provide older recipients with donor kidneys of a similar age, which may be expected to have high KDRI/KDPI scores. Without a randomized controlled trial, it is difficult to discern the isolated effect on patient and graft outcomes of transplanting a kidney with a high KDRI/KDPI score versus one with a lower KDRI/KDPI score.

Although the KDRI/KDPI was associated with graft failure in this cohort, discrimination for graft failure was poor, which most likely relates to differences in donor profile and graft failure rates between Ireland and the USA, where the score was derived. Given its predictive performance in this cohort, the suitability of the KDRI/KDPI in isolation for decisions regarding organ allocation and discarding in Ireland is questionable and thus it has not been adopted into clinical practice.

AUTHORS' CONTRIBUTIONS

All authors contributed to the research design and writing of the article. D.J.S. and P.O.K. contributed to data analysis. This was a retrospective analysis of the National Kidney Transplant Database. This database is managed by P.O.K. and P.J.C.

CONFLICT OF INTEREST STATEMENT

The authors confirm that there are no conflicts of interest. The results presented in this article have not been published previously in whole or part except in abstract form.

REFERENCES

1. Philipse E, Lee APK, Bracke B *et al.* Does Kidney Donor Risk Index implementation lead to the transplantation of more and higher-quality donor kidneys? *Nephrol Dial Transplant* 2017; 32: 1934–1938

2. US Department of Health and Human Services. Organ Procurement and Transplantation Network. 2017. https://optn.transplant.hrsa.gov
3. 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: 231–236
4. Stewart DE, Garcia VC, Aeder MI *et al*. New insights into the alleged kidney donor profile index labeling effect on kidney utilization. *Am J Transplant* 2017; 17: 2696–2704
5. Bertsimas D, Kung J, Trichakis N *et al*. Accept or decline? An analytics-based decision tool for kidney offer evaluation. *Transplantation* 2017; 101: 2898–2904
6. Rehse G, Halleck F, Khadzhynov D *et al*. Validation of the Living Kidney Donor Profile Index in a European cohort and comparison of long-term outcomes with US results. *Nephrol Dial Transplant* 2018; gfy118, doi: 10.1093/ndt/gfy118
7. 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: 2646–2653
8. Nazarian SM, Peng AW, Duggirala B *et al*. The kidney allocation system does not appropriately stratify risk of pediatric donor kidneys: implications for pediatric recipients. *Am J Transplant* 2018; 18: 574–579
9. Lehner LJ, Kleinsteuber A, Halleck F *et al*. Assessment of the Kidney Donor Profile Index in a European cohort. *Nephrol Dial Transplant* 2018; 33: 1465–1472
10. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med* 2006; 145: 21–29
11. Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. *Ann Intern Med* 2009; 150: 795–802
12. Rege A, Irish B, Castleberry A *et al*. Trends in usage and outcomes for expanded criteria donor kidney transplantation in the United States characterized by Kidney Donor Profile Index. *Cureus* 2016; 8: e887
13. Jay CL, Washburn K, Dean PG *et al*. Survival benefit in older patients associated with earlier transplant with high KDPI kidneys. *Transplantation* 2017; 101: 867–872
14. Doshi MD, Reese PP, Hall IE *et al*. Utility of applying quality assessment tools for kidneys with KDPI $\geq$80. *Transplantation* 2017; 101: 1125–1133
15. Traynor C, Saeed A, O'Ceallaigh E *et al*. Pre-transplant histology does not improve prediction of 5-year kidney allograft outcomes above and beyond clinical parameters. *Ren Fail* 2017; 39: 671–677
16. Peters-Sengers H, Heemskerk MBA, Geskus RB *et al*. Validation of the prognostic Kidney Donor Risk Index (KDRI) scoring system of deceased donors for renal transplantation in the Netherlands. *Transplantation* 2018; 102: 162–170
17. Parker WF, Thistlethwaite JR Jr, Ross LF. Kidney Donor Profile Index does not accurately predict the graft survival of pediatric deceased donor kidneys. *Transplantation* 2016; 100: 2471–2478
18. Alba AC, Agoritsas T, Walsh M *et al*. Discrimination and calibration of clinical prediction models: users' guides to the medical literature. *JAMA* 2017; 318: 1377–1384
19. Gandolfini I, Buzio C, Zanelli P *et al*. The Kidney Donor Profile Index (KDPI) of marginal donors allocated by standardized pretransplant donor biopsy assessment: distribution and association with graft outcomes. *Am J Transplant* 2014; 14: 2515–2525

Clinical Kidney Journal
ckj