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Original Article

ORIGINAL ARTICLE

Kidney Donor Profile Index and allograft outcomes: interactive effects of estimated post-transplant survival score and ischaemic time

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ABSTRACT

Background. The Kidney Donor Profile Index (KDPI) is routinely reported by the donation agencies in Australia. We determined the association between KDPI and short-term allograft loss and assessed if this association was modified by the estimated post-transplant survival (EPTS) score and total ischaemic time.

Methods. Using data from the Australia and New Zealand Dialysis and Transplant Registry, the association between KDPI (in quartiles) and 3-year overall allograft loss was examined using adjusted Cox regression analysis. The interactive effects between KDPI, EPTS score and total ischaemic time on allograft loss were assessed.

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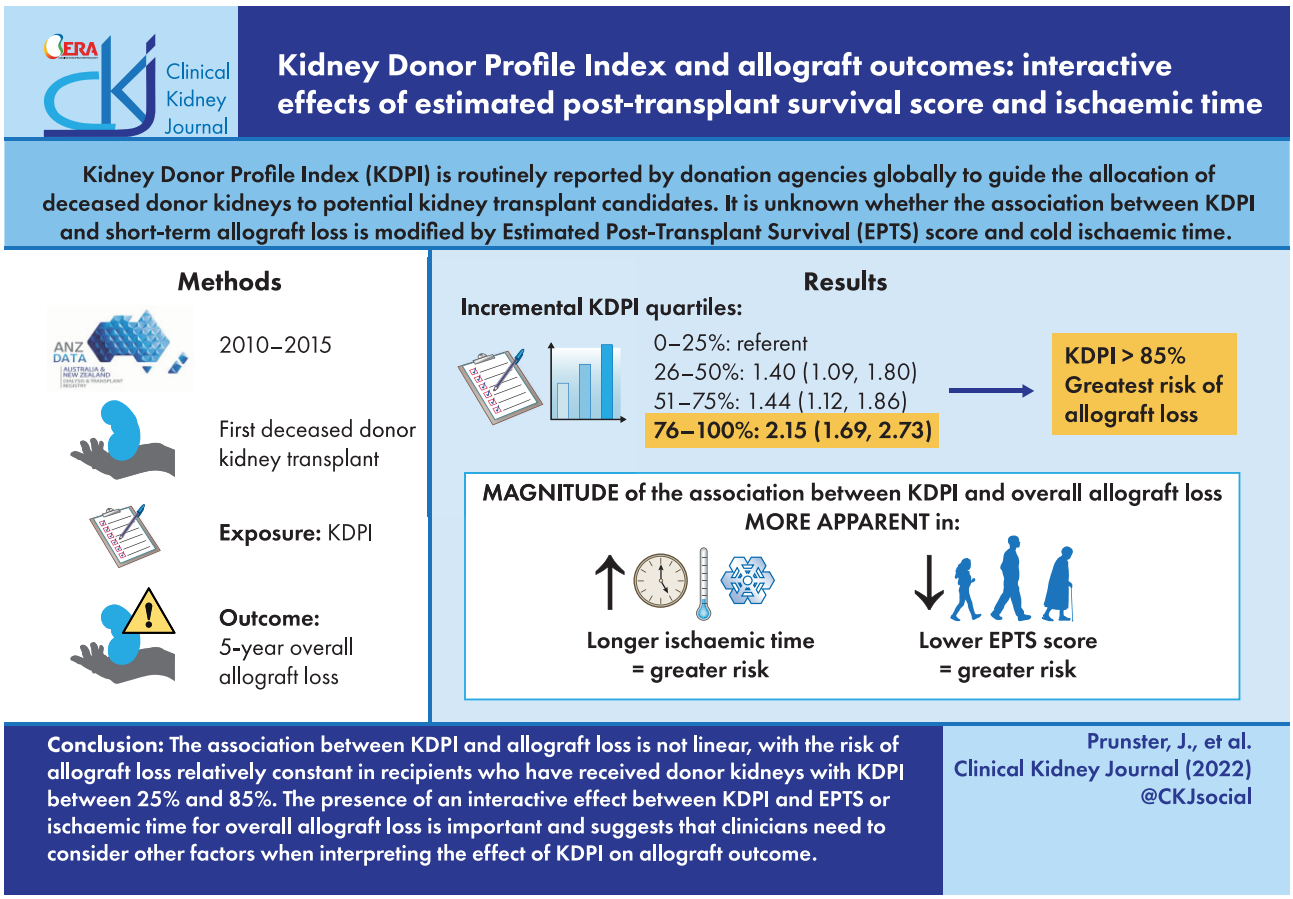
Results. Of 4006 deceased donor kidney transplant recipients transplanted between 2010 and 2015, 451 (11%) recipients experienced allograft loss within 3 years post-transplant. Compared with recipients of kidneys with a KDPI of 0–25%, recipients who received donor kidneys with a KDPI >75% experienced a 2-fold increased risk of 3-year allograft loss {adjusted hazard ratio [HR] 2.04 [95% confidence interval (CI) 1.53–2.71]}. The adjusted HRs for kidneys with a KDPI of 26–50% and 51–75% were 1.27 (95% CI 0.94–1.71) and 1.31 (95% CI 0.96–1.77), respectively. There were significant interactions between KDPI and EPTS scores (*P*-value for interaction <.01) and total ischaemic time (*P*-value for interaction <.01) such that the associations between higher KDPI quartiles and 3-year allograft loss were strongest in recipients with the lowest EPTS scores and longest total ischaemic time.

Conclusion. Recipients with higher post-transplant expected survival and transplants with longer total ischaemia who received donor allografts with higher KDPI scores experienced a greater risk of short-term allograft loss compared with those recipients with reduced post-transplant expected survival and with shorter total ischemia.

LAY SUMMARY

The ongoing disparity between donor organ availability and the increasing demand for donor kidneys for patients with kidney failure has resulted in an increased utilization of lower-quality donor kidneys for transplantation worldwide. The Kidney Donor Profile Index (KDPI) is a metric derived to improve the assessment of donor quality and prediction of kidney transplant outcome. In this article we show that non-donor factors such as lower patient survival score and longer ischaemic time adversely influence the relationship between the KDPI and transplant outcome such that clinicians have to be cognizant when interpreting the clinical applicability and significance of the KDPI.

GRAPHICAL ABSTRACT



Keywords: allograft loss, donor quality, EPTS, KDPI, kidney transplant

INTRODUCTION

The number of patients with kidney failure awaiting transplantation exceeds deceased donor organ availability. To address this disparity, the use of marginal donor kidneys for transplantation has increased worldwide. In Australia, the number of expanded criteria donors (ECDs) has substantially increased over the last decade, with similar trends observed in other countries, including the UK and Canada [1–3]. With concerns that the classification of deceased donor kidneys as ECD or non-ECD does not adequately characterise kidney quality [4, 5], the more granular Kidney Donor Risk Index (KDRI) was developed and shown to be superior in predicting allograft survival compared with the ECD classification [6].

The Kidney Donor Profile Index (KDPI) maps the KDRI of a donor on a percentage scale, such that lower and higher KDPI percentages correspond to higher- and lower-quality deceased donor kidneys, respectively, relative to the quality of deceased donor kidneys in the preceding 1–3 years [7, 8]. A KDPI score of 0% indicates a donor kidney that is expected to have better allograft survival than all other donor kidneys transplanted in the same year. In contrast, a KDPI score of 100% suggests that the kidney is projected to have the worst allograft survival compared with all other kidneys transplanted in that year. In the USA, the deceased donor kidney allocation system (KAS) was developed to improve the utility of deceased donor kidneys by preferentially allocating higher-quality donor kidneys to transplant candidates with the longest predicted post-transplant survival [9]. The KAS uses an estimated post-transplant survival (EPTS) score, which ranks candidates such that a lower percentage score represents a longer predicted post-transplant survival, whereas a higher percentage score represents a shorter expected post-transplant survival [10, 11].

Previous population cohort studies have shown that the acceptance of poorer-quality (higher KDPI) kidneys in younger or healthier recipients are associated with a greater allograft and patient survival disadvantage compared with older recipients or those with more comorbidities [12–16]. Consistent with this, there is a general reluctance among transplant clinicians in accepting these kidneys for healthier transplant candidates (lower EPTS scores) for fear that this may compromise long-term survival. Conversely, clinicians may also be apprehensive in allocating higher KDPI kidneys to older or less healthy transplant candidates (higher EPTS scores) with reduced functional reserve. Consequently, there are often practical difficulties in allocating higher KDPI kidneys for transplantation and some of these donor kidneys may be discarded unnecessarily. To provide guidance in this process, it is important to examine whether the health condition of potential kidney transplant candidates (with variable EPTS scores) or other modifiable transplant factors known to adversely affect allograft outcome, such as prolonged ischaemic time, influence allograft outcome in relation to KDPI.

The aims of this study were 2-fold. First, we aimed to determine the association between KDPI and short-term allograft outcome. Second, we aimed to establish whether EPTS or total ischaemic time modified the association between KDPI and allograft outcome.

MATERIALS AND METHODS

Study population

Using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, all adult patients (age ≥18 years) with kidney failure who received a first deceased donor kidney transplant in Australia between 2010 and 2015 with at least 3 years of follow-up data until 31 December 2018 were included. Recipients of multiple organ transplants, live-donor kidney transplants and deceased donors without available KDPI scores were excluded. The conduct of this study was approved by the University of Western Australia Human Research Ethics Committee, Perth, WA, Australia (ethics number RA/4/20/5936).

Exposure factor

The exposure was KDPI (in quartiles of 0–25%, 26–50%, 51–75% and >75%) derived from the Australian KDRI calculated using the formula:

$$\text{Exp}(-0.0194 \times \text{minimum (donor age} - 18, 0) + 0.0128 \times (\text{donor age} - 40) + 0.0107 \times \text{maximum (donor age} - 50, 0) + 0.126 \text{ (if donor has a history of treated hypertension)} + 0.130 \text{ (if donor has a history of diabetes)} + 0.220 \times ([\text{creatinine}/88.4] - 1) - 0.209 \times (\text{creatinine}/88.4) - 1.5) \text{ if (creatinine}/88.4) > 1.5 + 0.0881 \text{ if cause of death stroke (including spontaneous intracranial haemorrhage)} - 0.0464 \times ([\text{height} - 170]/10) - 0.0199 \times ((\text{weight} - 80)/5) \text{ if weight is less than 80 kg} + 0.133 \text{ (if planned donation pathway is donation after circulatory determination of death [DCDD])}.$$

The formula is available on the Transplantation Society of Australia and New Zealand (TSANZ) website and the KDRI is converted into KDPI (a percentile between 1 and 100%) [8].

Covariates

Two EPTS scores were calculated, with and without the inclusion of diabetes. The EPTS score without diabetes was calculated using the Australian EPTS (Aus-EPTS) score formula (available on the TSANZ website) [11]:

$$0.049 \times \text{maximum(age} - 25, 0) + 0.493 \times \text{prior kidney transplant} + 0.287 \times \log(\text{years on dialysis} + 1) + 0.598 \times (\text{years on dialysis} = 0),$$

with the derived raw EPTS score converted into an EPTS percentile between 1 and 100%.

The EPTS score with the inclusion of diabetes, as used in the KAS, was calculated as per the Organ Procurement and Transplant Network (OPTN-EPTS) [10]:

$$0.047 \times \text{maximum(age} - 25, 0) - 0.015 \times \text{diabetes} \times \text{maximum(age} - 25, 0) \times \text{prior organ transplant} - 0.237 \times \text{diabetes} \times \text{prior organ transplant} \times \log(\text{years on dialysis} + 1) - 0.099 \times \text{diabetes} \times \log(\text{years on dialysis} + 1) \times (\text{years on dialysis} = 0) - 0.348 \times \text{diabetes} \times (\text{years on dialysis} = 0) + 1.262 \times \text{diabetes}.$$

Other donor (sex, comorbid conditions and smoking history), recipient [sex, ethnicity, primary cause of kidney failure and presence of prevalent vascular diseases (coronary artery disease, cerebrovascular disease and peripheral vascular disease)] and transplant-related factors [human leucocyte antigen (HLA)-A, -B and -DR mismatches, total ischaemic time, percentage peak panel reactive antibody (PRA)] that were not included in the KDPI and EPTS calculation were also extracted from the ANZDATA Registry.

Outcome measures

The primary outcome was overall allograft loss at 3 and 5 years post-transplant. Secondary outcomes included death-censored

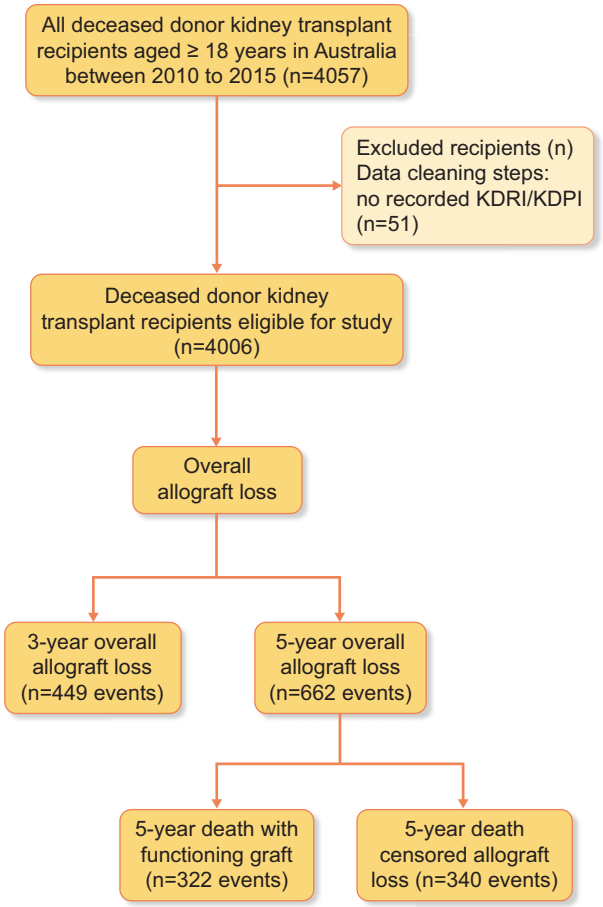


Figure 1: Flow diagram of the study cohort of 4006 deceased donor kidney transplant recipients in Australia between 2010 and 2015.

allograft loss and death with a functioning graft at 5 years post-transplant.

Statistical analysis

Data were expressed as number (%) for categorical variables or median [interquartile range (IQR)] for non-normally distributed continuous variables, with selected covariates compared between eras (2010–2012 and 2013–2015) using the chi-squared and Wilcoxon rank sum test where appropriate. The relationship between KDPI and KDRI was examined graphically using Loess curve fitting, with median (IQR) KDRIs reported for each KDPI quartile. The incidence rates of overall allograft loss at 3 and 5 years post-transplant were expressed as events [and 95% confidence intervals (CIs)] per 100 person-years for each KDPI quartile. The associations between KDPI quartiles and outcome measures were assessed using adjusted Cox regression models and results expressed as hazard ratios (HRs) and 95% CIs. The proportional hazards assumptions of the models were checked graphically by plotting the Schoenfeld residuals, and there were no violations for all models. Covariates in the multivariable models were selected *a priori*, which included KDPI, EPTS, recipient sex, ethnicity, cause of kidney failure, HLA mismatches, prevalent vascular disease and total ischaemic time. For the main models, the Aus-EPTS scores (without diabetes) were included in the analysis, with recipient diabetes status adjusted as a covariate. Plotted smoothed flexible adjusted HR curves with splined variables of KDPI showing the relationship between continuous KDPI and 3- and 5-year overall allograft loss were constructed. In a secondary analysis focusing on the cohort with KDPI >75%, the incidence rates and the associations between KDPI categories (in increments of 5%) and risks of overall allograft loss at 3 and 5 years were examined.

We constructed two 2-way interaction models between KDPI and EPTS categorised into three groups of 0–29, 30–79 and ≥80 for analysis, with thresholds determined by restricted cubic splines (Supplementary Fig. 1) and between KDPI and total ischaemic time (below and above a median of <12 h and ≥12 h) for 3- and 5-year risk of overall allograft loss. In addition, two sensitivity models were constructed to examine the associations between KDPI and EPTS with 3- and 5-year overall allograft loss: the substitution of the Aus-EPTS score for the OPTN-EPTS score and the exclusion of recipient diabetes status as a covariate (in the model with Aus-EPTS score). Statistical analysis was performed using Stata version 15.1 (StataCorp, College Station, TX, USA), with *P*-values <.05 considered statistically significant.

RESULTS

There were 4006 deceased donor kidney transplant recipients included in the study cohort (Fig. 1), with donor, recipient and transplant characteristics shown in Table 1. The median donor and recipient ages were 49 years (IQR 33–60) and 52 years (IQR 41–60), respectively. Cerebrovascular accident or intracranial/subarachnoid haemorrhage was the most common cause of deceased donor death, with 23% of donations after circulatory death. Almost 75% of recipients were Caucasian and 25% had prevalent diabetes at the time of transplantation.

Of the 4006 kidney transplant recipients, 1878 (47%) and 2128 (53%) were transplanted in 2010–2012 and 2013–2015, respectively. The median donor age [50 years (IQR 34–60) versus 48 years (IQR 33–59); $P = .04$] and recipient age [53 years (IQR 42–61) versus 51 years (IQR 41–60); $P = .01$] were higher in 2013–2015 compared with 2010–2012. A greater proportion of DCDD donor kidneys were transplanted in 2013–2015 compared with 2010–2012 (24% versus 21%; $P = .02$).

Over the study period, 451 (11%) and 662 (17%) recipients lost their allografts within 3 and 5 years post-transplant, respectively. The proportion of recipients who experienced allograft loss at 3 years (12% versus 11%; $P = .58$) and 5 years (18% versus 15%; $P = .06$) were similar in 2010–2012 and 2013–2015, respectively.

Supplementary Fig. 2 shows the relationship between continuous KDPI and KDRI. There was almost a linear relationship between KDPI and KDRI, except there was a greater respective corresponding reduction and increase in KDRI at the extremes of KDPI (<20% and >80%). The respective median KDRIs for KDPI quartiles 1, 2, 3 and 4 were 0.84 (IQR 0.79–0.91), 1.11 (IQR 1.05–1.18), 1.41 (IQR 1.32–1.51) and 1.94 (IQR 1.77–2.19).

Incidence rates of overall allograft loss

The incidence rates of overall allograft loss at 3 years post-transplant for recipients who received donor kidneys with a KDPI of 0–25% was 2.7 events/100 person-years (IQR 2.2–3.4). This compared with rates of 3.5 (IQR 2.9–4.3) for kidneys with a KDPI of 26–50%, 3.7 (IQR 3.0–4.5) for kidneys with a KDPI of 51–75% and 5.8 (IQR 5.0–6.8) for kidneys with a KDPI >75%. The

Table 1: Baseline characteristics of the study cohort between 2010 and 2015 (N = 4006).

Recipient characteristics	Value	Donor characteristics	Value
Recipient age (years), median (IQR)	52 (41–60)	Donor age (years), median (IQR)	49 (33–60)
Male, *n* (%)	2521 (62.9)	Male, *n* (%)	2226 (55.6)
Ethnicity, *n* (%)		Cause of death, *n* (%)	
White	2972 (74.1)	CVA/haemorrhage	1844 (46.0)
Indigenous Australian	167 (4.2)	Hypoxia/hanging	987 (24.6)
Asian	501 (12.5)	Other	1175 (29.4)
New Zealand Māori	103 (2.6)	Diabetes, *n* (%)	248 (6.2)
Other	263 (6.6)	Hypertension, *n* (%)	959 (23.9)
Primary cause of kidney failure, *n* (%)		Smoking history, *n* (%)	2433 (60.7)
Glomerulonephritis	1583 (39.5)	Donation after circulatory death, *n* (%)	917 (22.9)
Diabetes	749 (18.7)	KDRI, median (IQR)	1.3 (1.0–1.6)
Polycystic	507 (12.7)	KDPI, median (IQR)	51 (28–76)
Hypertension	274 (6.8)		
Reflux	267 (6.7)	Transplant characteristics	Value
Other	626 (15.6)	Total ischaemic time (hours), median (IQR)	12 (8–14)
Diabetes, *n* (%)	1012 (25.3)	HLA mismatches, median (IQR)	4 (2–5)
Coronary artery disease, *n* (%)	701 (17.5)	Peak PRA >80%, *n* (%)	139 (3.5)
Peripheral vascular disease, *n* (%)	321 (8.0)		
Cerebrovascular disease, *n* (%)	215 (5.4)	Transplant era, *n* (%)	Value
Duration of dialysis (years), median (IQR)	3.2 (1.6–5.4)	2010–2012	1878 (46.9)
EPTS score (diabetes included), median (IQR)	1.9 (1.4–2.4)	2013–2015	2128 (53.1)
EPTS percentile (diabetes included), median (IQR)	52 (28–77)		
EPTS score (diabetes excluded), median (IQR)	1.8 (1.2–2.2)		
EPTS percentile (diabetes excluded), median (IQR)	52 (26–76)		

CVA: cerebrovascular accident.

respective incidence rates of overall allograft loss at 5 years were 2.6 (IQR 2.2–3.1), 3.6 (IQR 3.1–4.2), 3.8 (IQR 3.2–4.4) and 5.7 (IQR 5.0–6.4) events/100 person-years.

Association between KDPI in quartiles and overall allograft loss

Over the median follow-up period of 5.1 years (IQR 3.6–6.8), 451 (11.3%) and 662 (16.5%) recipients experienced allograft loss within 3 and 5 years post-transplant, respectively. Table 2 shows the adjusted estimates of the association between KDPI quartiles and other covariates for overall allograft loss. Compared with recipients of kidneys with a KDPI of 0–25%, only kidneys with a KDPI >75% were associated with an increased risk of 3- and 5-year overall allograft loss. Figs. 2A and B show the plots of the adjusted HRs between continuous KDPI and overall allograft loss at 3 and 5 years, respectively, with a median KDPI of 50% as the reference point. For both plots, the inflection points towards lower and higher HRs occurred at KDPIs of <20% and >80%, respectively.

Association between KDPI >75% and overall allograft loss

Table 3 shows the incidence rates and adjusted HRs of the association between incremental KDPI categories >75% and overall allograft loss. The incidence rates of allograft loss at 5 years were 4–5/100 person-years for kidneys with a KDPI of 76–85%, increasing to 7/100 person-years for kidneys with a KDPI >85%. Compared with recipients of kidneys with a KDPI of 76–80%, kidneys with a KDPI of 86–100% were associated with a greater risk of allograft loss at 3 and 5 years. The incidence rates and risk of allograft loss were similar between recipients of kidneys with a KDPI of 51–85%.

Association between KDPI, death-censored allograft loss and death with a functioning graft

Table 2 shows the associations between KDPI and 5-year risk of death-censored allograft loss and death with a functioning graft. Compared with kidneys with a KDPI of 0–25%, there was a greater risk of death-censored allograft loss with KDPI quartiles >25%, whereas for death with a functioning graft, only kidneys in the highest KDPI quartile of >75% were associated with an increased risk.

Interactive effect between KDPI and EPTS for overall allograft loss

EPTS moderated the interactive effect between donor KDPI and overall allograft loss at 3 and 5 years (P-values for interaction <.001). Fig. 3 shows the adjusted HRs for KDPI quartiles for 3- and 5-year allograft loss, stratified by EPTS categories. Compared with recipients who received kidneys from donors with a KDPI of 0–25%, those who received kidneys with a higher KDPI were more likely to experience allograft loss at 3 and/or 5 years, with relative estimates higher for recipients with lower EPTS scores.

Fig. 4A and B shows the incidence rates of overall allograft loss at 3 and 5 years post-transplant, respectively, according to the pre-specified EPTS categories. For each EPTS category, the incidence rates for 3- and 5-year overall allograft loss were highest for the fourth KDPI quartiles, although incidence rates for overall allograft loss for the middle two quartiles of 26–50% and 51–75% were similar.

Interactive effect between KDPI and total ischaemic time for overall allograft loss

Concerning the interactive effect, total ischaemic time moderated the association between donor KDPI and overall allograft

Table 2: Associations between KDPI and EPTS scores and risks of overall allograft loss at 3 and 5 years after kidney transplantation.

Characteristics	3-year overall allograft loss, adjusted HR (95% CI)	5-year overall allograft loss, adjusted HR (95% CI)
KDPI (%)		
0–25	1.00	1.00
>25–50	1.27 (0.94–1.71)	1.40 (1.09–1.80)
>50–75	1.31 (0.96–1.77)	1.44 (1.12–1.86)
>75	2.04 (1.53–2.71)	2.15 (1.69–2.73)
EPTS score (%)		
≤30	1.00	1.00
>30–80	1.03 (0.81–1.32)	0.96 (0.79–1.18)
>80	1.40 (1.06–1.85)	1.42 (1.13–1.78)
Female	0.90 (0.74–1.11)	0.91 (0.77–1.07)
Coronary artery disease	1.31 (1.04–1.66)	1.35 (1.11–1.64)
Peripheral vascular disease	1.20 (0.88–1.65)	1.10 (0.84–1.44)
Cerebrovascular disease	1.44 (1.03–2.03)	1.39 (1.04–1.85)
Diabetes	1.10 (0.77–1.59)	1.10 (0.81–1.48)
Ethnicity		
White	1.00	1.00
Indigenous Australian	1.17 (0.76–1.82)	1.57 (1.13–2.18)
Asian	0.76 (0.55–1.04)	0.69 (0.52–0.90)
New Zealand Māori	1.31 (0.78–2.22)	1.53 (1.02–2.31)
Other	1.31 (0.93–1.85)	1.24 (0.92–1.66)
Cause of kidney failure		
Glomerulonephritis	1.00	1.00
Diabetes	1.14 (0.75–1.72)	1.12 (0.80–1.59)
Polycystic kidney disease	0.53 (0.35–0.80)	0.60 (0.44–0.82)
Hypertension/vascular	1.20 (0.84–1.71)	1.05 (0.77–1.42)
Reflux	1.20 (0.81–1.77)	1.09 (0.79–1.51)
Other	1.23 (0.94–1.63)	1.18 (0.94–1.48)
HLA mismatches (per mismatch)	1.05 (0.99–1.11)	1.03 (0.98–1.08)
Total ischaemic time (per minute increase)	1.05 (0.86–1.27)	1.06 (0.90–1.24)
	5-year death-censored allograft loss, adjusted HR (95% CI)	5-year death with a functioning graft, adjusted HR (95% CI)
KDPI (%)		
0–25	1.00	1.00
>25–50	1.46 (1.03–2.08)	1.29 (0.94–1.76)
>50–75	1.56 (1.09–2.23)	1.27 (0.93–1.74)
>75	2.60 (1.86–3.64)	1.58 (1.16–2.14)
EPTS score (%)		
≤30	1.00	1.00
>30–80	0.71 (0.55–0.92)	2.11 (1.51–2.95)
>80	0.57 (0.40–0.80)	4.35 (3.07–6.16)
Female	0.93 (0.74–1.17)	0.80 (0.64–1.00)
Coronary artery disease	0.94 (0.69–1.29)	1.60 (1.28–2.02)
Peripheral vascular disease	1.42 (0.96–2.11)	1.07 (0.77–1.47)
Cerebrovascular disease	1.05 (0.64–1.72)	1.47 (1.05–2.05)
Diabetes	1.31 (0.87–1.96)	1.20 (0.83–1.74)
Ethnicity		
White	1.00	1.00
Indigenous Australian	1.89 (1.25–2.87)	1.09 (0.66–1.80)
Asian	0.89 (0.62–1.28)	0.51 (0.35–0.74)
New Zealand Māori	2.11 (1.24–3.58)	1.13 (0.65–1.95)
Other	1.77 (1.23–2.55)	0.76 (0.48–1.20)
Cause of kidney failure		
Glomerulonephritis	1.00	1.00
Diabetes	0.73 (0.45–1.19)	1.31 (0.86–2.00)
Polycystic kidney disease	0.53 (0.33–0.85)	0.71 (0.49–1.02)
Hypertension/vascular	0.99 (0.63–1.57)	1.07 (0.74–1.56)
Reflux	1.17 (0.77–1.78)	1.09 (0.70–1.68)
Other	1.09 (0.80–1.49)	1.29 (0.96–1.73)
HLA mismatches (per mismatch)	1.08 (1.01–1.16)	0.98 (0.93–1.04)
Total ischaemic time (per minute increase)	1.13 (0.90–1.41)	1.11 (0.91–1.35)

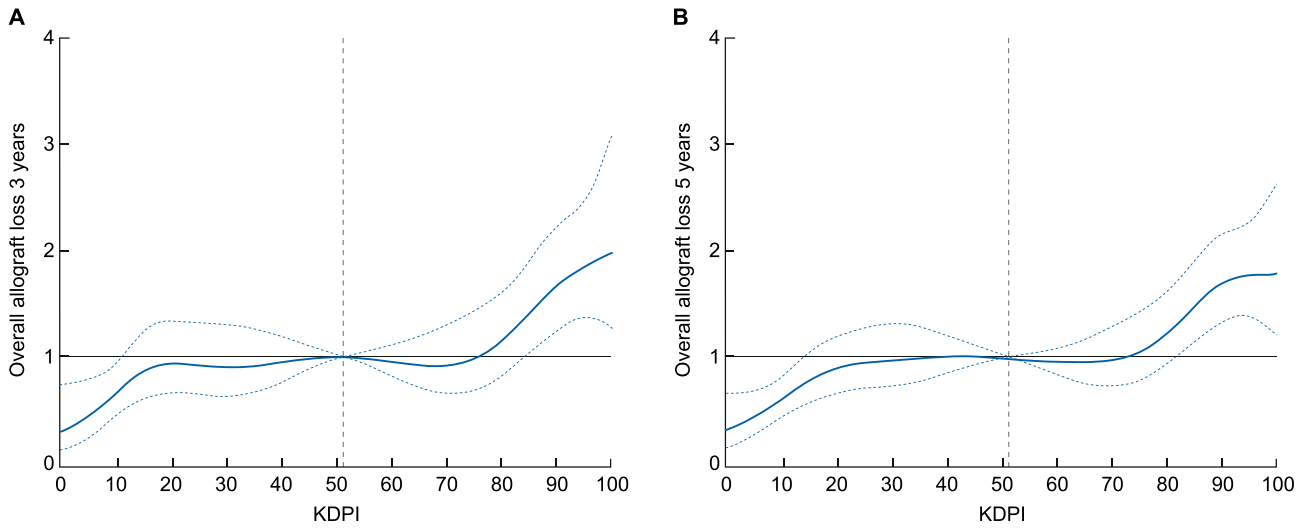


Figure 2: Smoothed flexible adjusted HR curves for **(A)** 3- and **(B)** 5-year overall allograft loss with splined variables of continuous KDPI. The continuous blue line represents the plotted adjusted HRs and the discontinuous black lines represent the 95% CIs.

Table 3: Incidence rates and the risk of allograft loss at 3 and 5 years of donor kidneys with a KDPI >75%.

KDPI 76–100% (referent KDPI 76–80%)	Allograft loss at 3 years		Allograft loss at 5 years	
	Incidence rates[a]	Adjusted HR (95% CI)	Incidence rates[a]	Adjusted HR (95% CI)
76–80% ($n = 182$)	3.7 (2.4–5.8)	1.00	3.7 (2.5–5.3)	1.00
81–85% ($n = 210$)	4.4 (2.9–6.4)	1.13 (0.62–2.06)	4.8 (3.6–6.6)	1.27 (0.78–2.05)
86–90% ($n = 222$)	6.6 (4.8–9.0)	1.71 (0.98–2.98)	6.9 (5.3–8.9)	1.88 (1.19–2.97)
91–95% ($n = 206$)	6.5 (4.7–9.1)	1.72 (0.98–3.00)	5.4 (4.1–7.3)	1.47 (0.91–2.37)
96–100% ($n = 213$)	7.7 (5.8–10.4)	1.95 (1.13–3.37)	7.2 (5.6–9.3)	1.86 (1.18–2.93)
KDPI 51–100% (referent KDPI 51–75%)[b]	Allograft loss at 3 years		Allograft loss at 5 years	
	Incidence rates[a]	Adjusted HR (95% CI)	Incidence rates[a]	Adjusted HR (95% CI)
51–75% ($n = 1004$)	3.7 (3.0–4.5)	1.00	3.8 (3.2–4.4)	1.00
76–80% ($n = 182$)	3.7 (2.4–5.8)	1.01 (0.62–1.65)	3.7 (2.5–5.3)	0.98 (0.65–1.46)
81–85% ($n = 210$)	4.4 (2.9–6.4)	1.19 (0.76–1.84)	4.8 (3.6–6.6)	1.30 (0.92–1.83)
86–90% ($n = 222$)	6.6 (4.8–9.0)	1.74 (1.20–2.52)	6.9 (5.3–8.9)	1.83 (1.35–2.48)
91–95% ($n = 206$)	6.5 (4.7–9.1)	1.73 (1.18–2.53)	5.4 (4.1–7.3)	1.44 (1.03–2.02)
96–100% ($n = 213$)	7.7 (5.8–10.4)	2.00 (1.39–2.87)	7.2 (5.6–9.3)	1.84 (1.36–2.50)

[a]Data expressed as events per 100 person-years.
[b]Model with referent KDPI of 51–75%.

loss at 3 and 5 years (*P*-values for interaction <.001). In recipients who received transplants with an ischaemic time of at least 12 h, donor KDPIs of 26–50%, 51–75% and >75% were associated with adjusted HR for 5-year allograft loss [1.97 (95% CI 1.30–2.98), 1.78 (95% CI 1.17–2.71) and 2.52 (95% CI 1.69–3.76), respectively] compared with a donor KDPI of 0–25%. In contrast, there were no significant associations between a donor KDPI of 26–75% in recipients who received transplants with an ischaemic time of less than 12 h. Fig. 3 shows the adjusted HRs for KDPI quartiles for 3- and 5-year allograft loss, stratified by median total ischaemic time. The incidence rates of overall allograft loss at 3 and 5 years post-transplant, according to KDPI quartiles and median total ischaemic time, are shown in Figs. 5A and B, respectively.

Sensitivity analysis

Supplementary Table 1 shows the association between KDPI quartiles and the risk of 3- and 5-year overall allograft loss. The estimates of the association between KDPI quartiles and allograft loss were similar in the models that included the Aus-EPTS score (with inclusion and exclusion of diabetes as a covariate) or OPTN-EPTS score. The inclusion and exclusion of recipient diabetes status as a covariate did not change the adjusted estimates of the association between Aus-EPTS categories and overall allograft loss at 3 and 5 years post-transplant.

DISCUSSION

With implementation of the allocation policy in Australia to include KDPI score, it is essential to evaluate the association between KDPI and allograft outcome and to define whether there are non-donor factors that may modify this association. There were three notable findings of clinical relevance. First, the incidence rates and risk of allograft loss appeared relatively constant in recipients who have received donor kidneys with a KDPI of 25–85%. Second, recipients who received a donor kidneys with

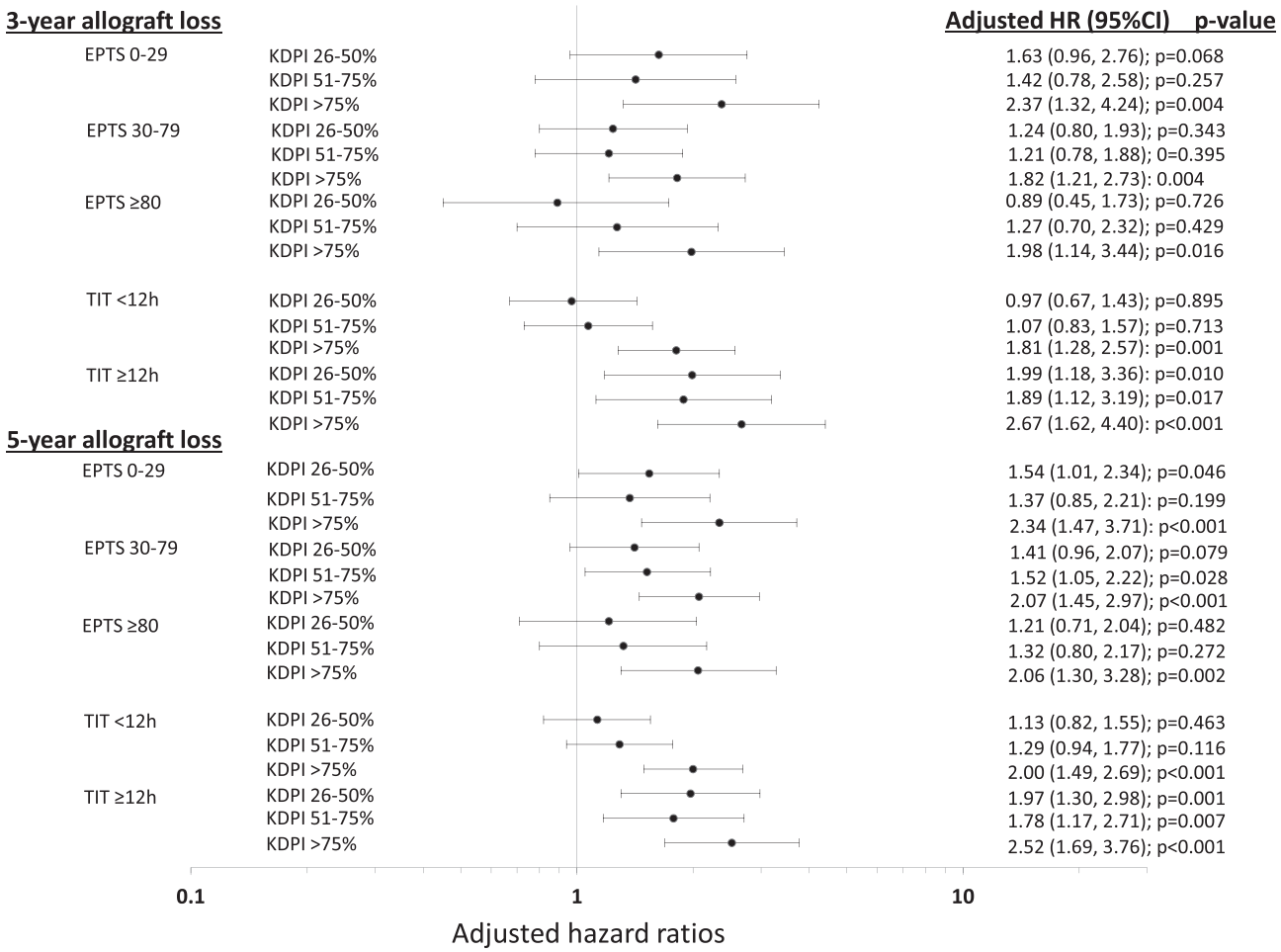


Figure 3: Forest plots showing the adjusted HRs with 95% CIs of the associations between KDPI quartiles and the 3- and 5-year risk of overall allograft loss, stratified by EPTS categories and median total ischaemic time (TIT) in the Cox regression models.

higher KDPI scores experienced a higher risk of allograft loss, and this association was modified by the total ischaemia time and the post-transplant expected survival of the recipients. The greatest risk of allograft loss was seen in recipients with the lowest EPTS score (recipients with favourable post-transplant prognosis) and kidneys with the longest total ischaemia time. Third, the exclusion of recipient diabetes status from the Aus-EPTS score did not influence the associations between KDPI or EPTS and allograft outcomes.

The KDRI/KDPI was developed as a more accurate metric of donor quality, calculated using an equation that considers a combination of donor and transplant factors with prognostic significance for allograft outcome. These indices have been relied upon to ensure a more equitable distribution of deceased donor kidneys based on the association with allograft loss in time-to-event models. Even though the KDRI/KDPI scores are derived using outcome data from local population cohorts, external validation of these scores has been undertaken in other populations [17–19]. For example, the US and UK KDRI/KDPI scores have been shown to improve discrimination for allograft outcomes in Australia and New Zealand, but the C-statistics of these models were generally <0.65 [17]. The validation of the US KDRI/KDPI score to predict allograft outcomes has been shown for other population cohorts, including Canada and Ireland, but it remains debatable whether these scores substantially improve discrimination for allograft outcome beyond donor age alone [18, 19]. In our study, the association between KDPI and allograft loss appeared non-linear, with only the extremes of KDPI showing significant predictive ability in discriminating allograft loss. There was little to no change in the relative hazards of allograft loss of kidneys with a KDPI of 25–85%, suggesting that clinicians should be aware of the limitations of using this numerical metric of donor quality in the decision-making process of accepting/declining certain donor kidneys for potential kidney transplant candidates.

Similar to the US-derived KDRI/KDPI scores, the US-derived EPTS score has been shown to improve discrimination in predicting post-transplant survival in external population cohorts, with C-statistics approaching 0.70 [20, 21]. However, it must be emphasized that there are variations in the derivation of the EPTS score. In contrast to the US-derived EPTS score, the Australian EPTS score omits diabetes status, whereas the Korean EPTS score omits prior transplant status but includes hepatitis C status [20, 22]. Diabetes status has been consistently shown to be an important predictor of long-term allograft and patient survival in dialysis and kidney transplant recipients [23, 24].

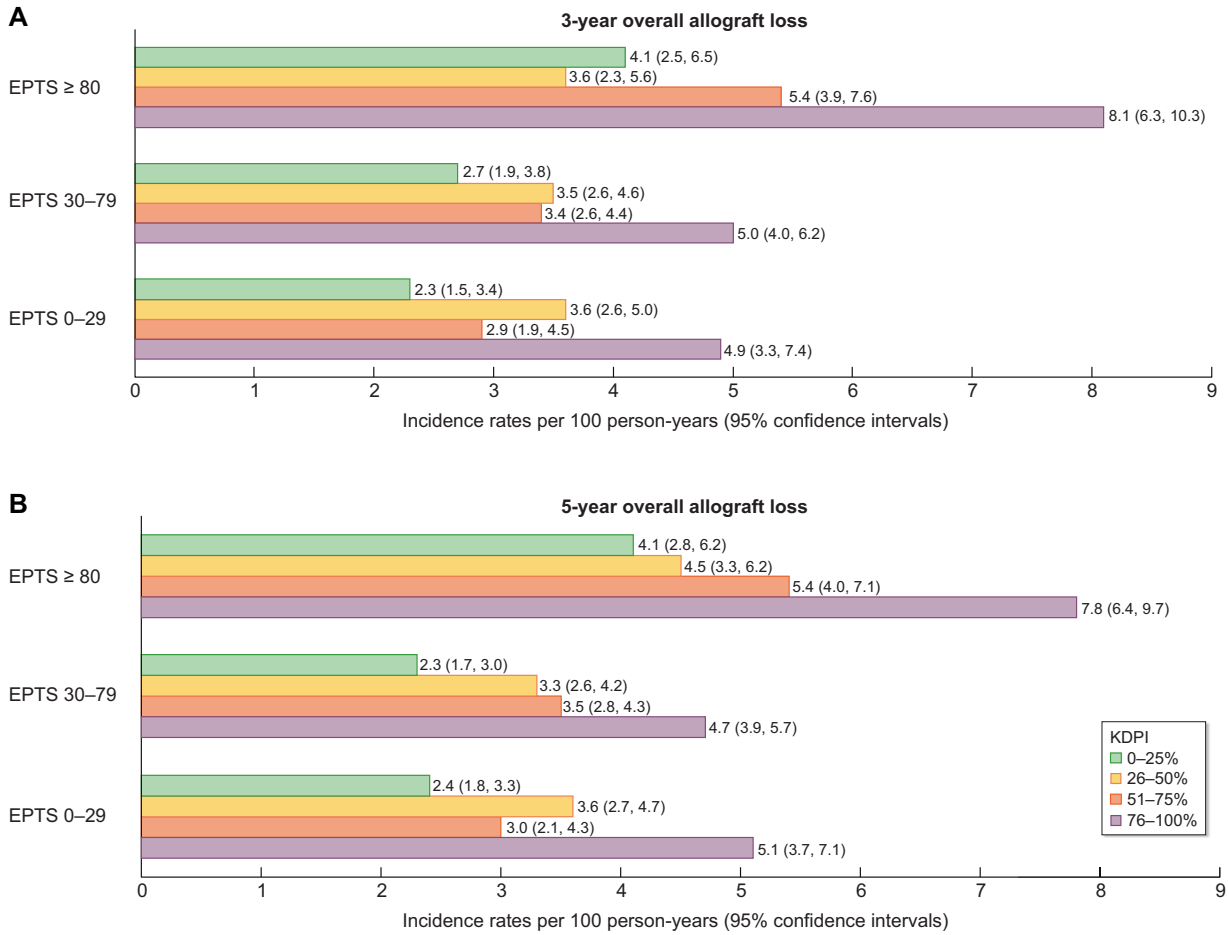


Figure 4: Bar graph showing the incidence rates (expressed as events/100 person-years) of **(A)** 3- and **(B)** 5-year overall allograft loss for accepting donor kidneys with a KDPI of 0–25%, 26–50%, 51–75% and >75%, according to recipients with EPTS scores (without the inclusion of diabetes status) of 0–29, 30–79 and ≥80.

However, the inclusion of recipient diabetes status in the EPTS score (or as a covariate in the model with Aus-EPTS) did not appreciably improve the prediction of KDPI or EPTS for overall allograft loss and therefore diabetes status was not considered in the calculation of the Aus-EPTS score.

It is important to take into consideration that neither the KDPI or the EPTS include all clinically relevant predictors of allograft and patient outcomes. Furthermore, these scores do not take into consideration the impact on allograft outcome of the immunological risk profile, likelihood of and expected waiting time for a future better-quality donor kidney offer (i.e. the 'trade-off' of additional waiting time) and the deleterious effect of prolonged total ischaemic time. This, together with the potential effect modification by these factors, limits the clinical utility of KDPI/EPTS in isolation. The finding that EPTS and total ischaemic time modified the association between KDPI and allograft loss is not unexpected. Prior publications have shown that recipient age and total ischaemic time modified the association between ECD status, allograft and patient outcomes such that the association between older donors/ECD status and poorer allograft and/or patient survival were more apparent for younger recipients and extended total ischaemic time [12, 25]. KDPI and EPTS scores are derived from kidney transplant recipient outcome data for the preceding 1–3 years. Given the temporal change and lack of precise and in-depth details of donor and recipient characteristics available in registry data, it is not surprising that these scores may not always predict short-term allograft and patient outcomes with high accuracy. Despite these caveats, the KDPI and EPTS scores are now explicitly considered in several national algorithms when allocating deceased donor kidneys, to avoid allocating high- and low-KDPI kidneys to patients with low and high EPTS scores, respectively. The use of these scores in kidney allocation appears rational given their association with allograft outcomes at the extremes of the KDPI and EPTS ranges.

There are some limitations to the data presented. We have only examined short- to medium-term allograft and patient outcomes and the association between KDPI or EPTS; longer-term outcomes have not been evaluated. In this study we used the OPTN equation to calculate the EPTS diabetes score, but this score has not been validated in non-US populations. In addition, it is likely that post-transplant complications such as delayed graft function, acute rejection and allograft function may influence allograft outcomes, but these were not examined in this study.

Even though KDPI may be considered a better metric of donor quality, it is evident that the association with short- and medium-term allograft outcome is not clearly linear, with the differences in allograft outcome observed at the extremes of this metric. The presence of an interactive effect between KDPI and

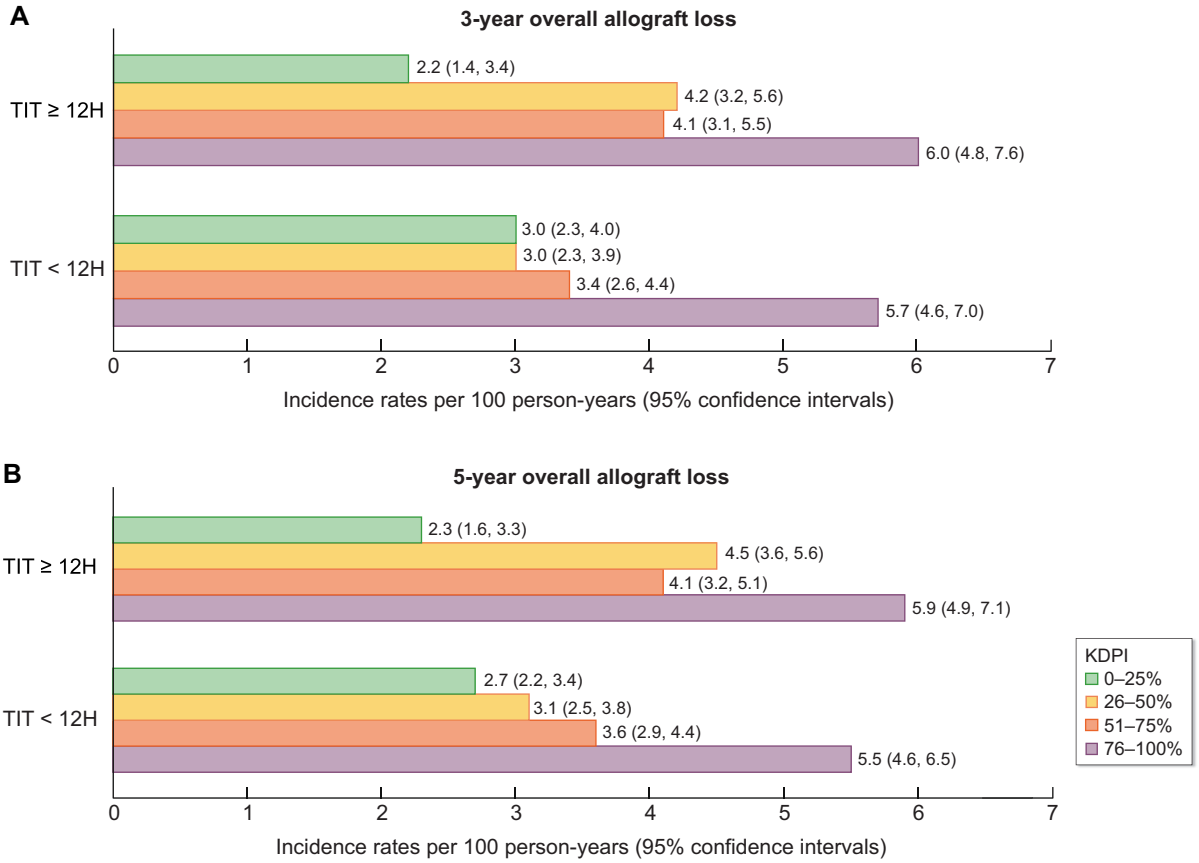


Figure 5: Bar graph showing the incidence rates (expressed as events/100 person-years) of **(A)** 3- and **(B)** 5-year overall allograft loss for accepting donor kidneys with a KDPI of 0–25%, 26–50%, 51–75% and >75%, according to the median total ischaemic time (TIT) of <12 h and ≥12 h.

EPTS or total ischaemic time for overall allograft loss is of clinical importance and suggests that clinicians need to consider other factors when interpreting the effect of KDPI on allograft outcome. Understanding these and other limitations in the application of KDPI and EPTS thresholds is critical to avoid unnecessary refusal of appropriate donor organs for patients on the waiting list.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

W.L. and J.P. conceptualized the project. W.L. and E.O. performed the analysis. All reviewed and wrote the paper.

DATA AVAILABILITY STATEMENT

Data used for analysis in this article can be requested from the ANZDATA Registry (requests@anzdata.org.au).

CONFLICT OF INTEREST STATEMENT

None declared.

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