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Assessing survival post-kidney transplantation in Australia: A multivariable prediction model

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Abstract

Aim: Kidney transplantation remains the preferred standard of care for patients with kidney failure. Most patients do not access this treatment and wide variations exist in which patients access transplantation. We sought to develop a model to estimate post-kidney transplant survival to inform more accurate comparisons of access to kidney transplantation.

Methods: Development and validation of prediction models using demographic and clinical data from the Australia and New Zealand Dialysis and Transplant Registry. Adult deceased donor kidney only transplant recipients between 2000 and 2020 were included. Cox proportional hazards regression methods were used with a primary outcome of patient survival. Models were evaluated using Harrell's C-statistic for discrimination, and calibration plots, predicted survival probabilities and Akaike Information Criterion for goodness-of-fit.

Results: The model development and validation cohorts included 11 302 participants. Most participants were male (62.8%) and Caucasian (79.2%). Glomerulonephritis was the most common cause of kidney disease (45.6%). The final model included recipient, donor, and transplant related variables. The model had good discrimination (C-statistic, 0.72; 95% confidence interval (CI) 0.70–0.74 in the development cohort, 0.70; 95% CI 0.67–0.73 in the validation cohort and 0.72; 95% CI 0.69–0.75 in the temporal cohort) and was well calibrated.

Conclusion: We developed a statistical model that predicts post-kidney transplant survival in Australian kidney failure patients. This model will aid in assessing the suitability of kidney transplantation for patients with kidney failure. Survival estimates can be used to make more informed comparisons of access to transplantation between units to better measure equity of access to organ transplantation.

KEYWORDS
kidney transplantation, risk assessment, survival models

Summary at a glance

Kidney transplantation remains the gold standard treatment for kidney failure. However, only a limited number of patients access transplantation. This paper outlines a model that predicts post-kidney transplant survival. Survival estimates will inform assessments of patient suitability for transplant and aid in comparing access to transplantation between different centres.

1 | INTRODUCTION

Kidney transplantation is a highly effective treatment for kidney failure and remains the preferred standard of care for most patients.[1,2] Concerningly, wide variations exist in which patients access kidney transplantation.[2–4] For an Australian patient starting kidney replacement therapy, their chance of being wait-listed or transplanted at 1-year after starting treatment can range from 0% to 100% depending on the location of their treatment.[3] Prior analyses have identified factors such as patient gender, ethnicity and geographical location may be associated with variations in access to kidney transplantation.[2] The identification of variations related to these factors have raised concerns that specific sub-groups of patients may face higher barriers to accessing kidney transplantation than others. This has prompted calls for further analyses to determine if these observed differences represent inequitable variations in clinical practice or if other unmeasured factors are at play.[2,5,6]

Prior analyses that have assessed variations in access to waitlisting and kidney transplantation have focused on all patients receiving dialysis treatments, or an age restricted group.[3] Whilst kidney transplantation may benefit many patients, there are a pool of patients receiving kidney replacement therapy who may not benefit from transplantation and may be inappropriate for referral and waitlisting. Currently, the inclusion of these patients in analyses of access to waitlisting and transplant may bias comparisons between different centres. To overcome this, methods to identify a target population of kidney failure patients who are potentially transplant eligible and likely to benefit from transplantation are required to make more informed comparisons.[7]

The complexity of assessing eligibility for kidney transplantation must be considered when seeking to identify potentially transplant eligible patients. This complexity lies in the dynamic interplay of patient and system factors that influence whether a patient may be added to the kidney transplant waiting list. Transplant centres and clinicians may place varying levels of importance on specific patient and system factors when determining patient eligibility and this may mean acceptance criteria differ between or within transplant units. Due to these differences, it is difficult to apply blanket suitability criteria at a system level. A key element of agreement is the importance of patient survival post-kidney transplantation. Patient survival is universally highlighted as an important factor across all assessment guidelines and represents a consistent starting point for identifying potentially transplant eligible patients.[7,8]

Pre-existing statistical models have been developed to estimate post-kidney transplant survival, however none have been developed using Australian patient data.[9] In Australia, distinct differences exist in kidney failure patient demographics, post-kidney transplant outcomes and health policy settings. These differences are particularly notable in relation to the USA where most post-transplant survival models have been developed. Most importantly, the incidence of treated kidney failure is substantially lower in Australia compared to the USA, Canada, and many Asian countries.[10] Recipients of kidney transplants in Australia also enjoy a significant graft-survival advantage compared to the USA with median survival of greater than 14.7 years compared with 11.2 years.[11] Australian transplant patients also benefit from universal healthcare coverage. Conversely, access to pre-emptive transplantation is restricted to living kidney donor transplants.[12] Distinct differences in transplant access and outcomes also exist for Australian First Nations patients with kidney failure.[12] These differences necessitate developing and validating locally customised models of patient survival.

Our study focused on individuals with kidney disease receiving kidney replacement therapy in Australia. Our aim was to develop a statistical model predicting post-kidney transplant survival. This model will aid in assessing the suitability of kidney transplantation for patients with kidney failure. By using this model, we can remove patient survival as a potential confounder when comparing different transplant units. This will enable more accurate and informed comparisons of access to transplantation. This will better inform our understanding of observed disparities in transplant access and ensure equity is achieved across the kidney transplant system.

2 | METHODS

2.1 | Data source and study population

Data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry was used for this analysis. The ANZDATA Registry is a clinical quality registry that collects data on patients with kidney failure receiving kidney replacement therapies in Australia & New Zealand. The registry achieves near complete (>98%) data capture for patients with kidney failure in Australia & New Zealand.[12]

Patients were included if they were 18 years or above and underwent a deceased donor kidney transplant in Australia between January 1st 2000 and December 31st 2020. Recipients of living donor, multi-organ or transplants performed overseas were excluded from the analysis. Study follow-up was through to 31st December 2014 for the development cohort and at 31st December 2020 for the temporal validation cohort or at loss to follow-up.

2.2 | Statistical analysis

The characteristics of the study cohort were described using means and standard deviations, or median values with interquartile ranges, for continuous variables, and proportions were used for categorical variables.

The patient cohort was separated into two groups, a development cohort and temporal validation cohort, Figure 1. The model development cohort included patients who were registered in ANZDATA and underwent deceased donor kidney transplantation between January 1st 2000 and December 31st 2014. The temporal validation cohort included patients who were registered in ANZDATA and underwent deceased donor kidney transplantation between January 1st 2015 and December 31st 2020. Differences between the development and temporal validation cohorts were tested using a two-sided t-test for normally distributed continuous variables, Wilcoxon Rank Sum Test for non-normally distributed continuous variables and Chi squared test for categorical variables.

2.3 | Model development

The model development cohort was randomly split 2:1 into a derivation and validation cohort, Figure 1.[13] The split was stratified by age group, ethnicity, diabetes status and donor type (donation after neurological determination of death versus donation after circulatory death). The model derivation cohort was used to develop the base model and this model was then validated in the base validation cohort.

The primary outcome was patient survival after kidney transplantation. Patient survival was calculated by time from kidney transplantation to death as recorded in the ANZDATA Registry. Covariates utilised during model development comprised of recipient, donor, and transplant factors. Recipient factors included age, sex, ethnicity, primary kidney disease, comorbid conditions (diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and chronic lung disease), duration of kidney replacement therapy, body mass index (BMI) and smoking history. Donor factors included donor age, sex, ethnicity, diabetes status, donation after circulatory death status, cause of death, body mass index, history of malignancy and hypertension status. Transplant factors included the number of human-leukocyte antigen (HLA) mismatches, ischaemic time, transplant era, recipient-donor BMI mismatch and peak panel reactive antibody (PRA).

All included variables were tested using univariate Cox proportional hazards models. All factors were included in a multivariate base

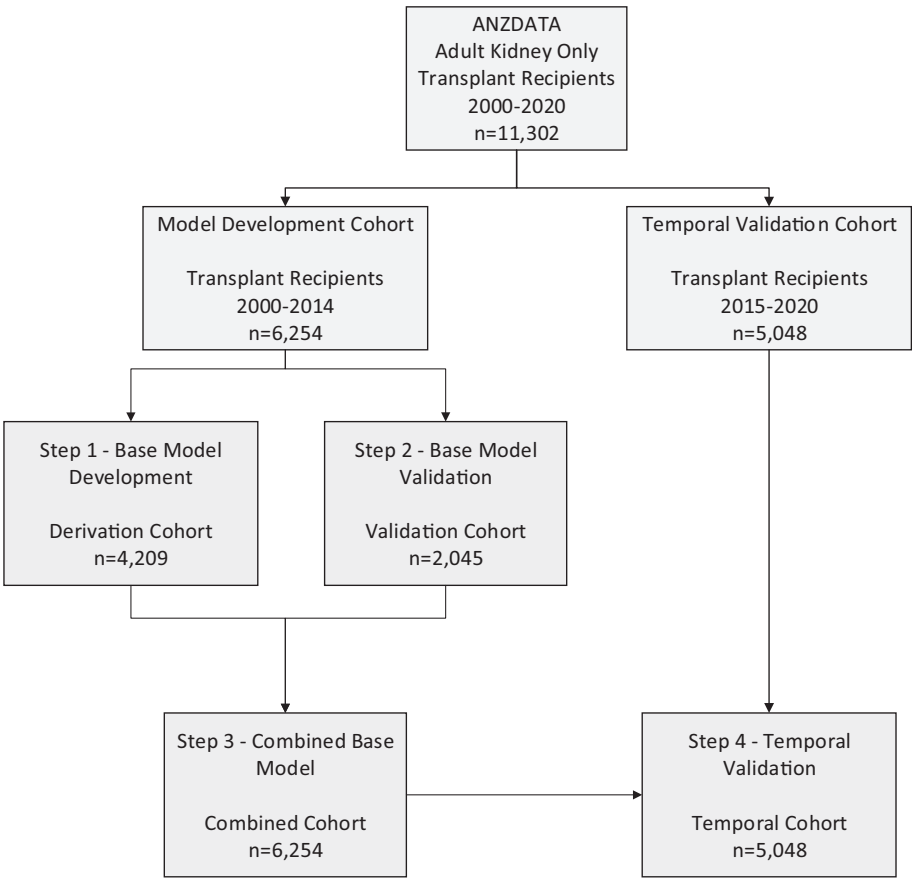

FIGURE 1 Study flow diagram.

model if they were significant ($p < .20$) on univariate analysis or were deemed clinically relevant.[14] 2-way interaction testing was performed to assess for effect modification of all included variables in the base model. Significant interaction terms were included in subsequent models and compared with the base model using Akaike's information criterion (AIC) and Harrell's C-statistic. Non-significant factors were then removed from the model through backwards selection until all factors were significant at a level of $p < .05$ or considered clinically significant. Missing data was not reclassified. The base model was then validated in the base model validation cohort, Figure 1. Estimates obtained from the derivation model were used to predict survival in the base validation cohort and model performance was assessed. Once model performance was tested in the base validation cohort new point estimates were generated from a combined cohort including the base derivation and validation cohorts to improve the accuracy of the point estimates. The proportional hazards assumption was examined using Schoenfeld residuals.

2.4 | Model validation

The combined base model was then validated in the temporal validation cohort, Figure 1. Estimates obtained from the combined base model were used to predict survival in the temporal cohort. Model performance was tested by reviewing model fit, discrimination, the ability of the model to differentiate between patients who survived and those who did not, and calibration, how accurate model estimates are against actual observed survival in the validation dataset using methodology described by Royston.[15] For the purposes of validating our model, patients were split into risk quintiles of predicted 5-year post-kidney transplant survival (<80%, 80%–84%, 85%–89%, 90%–94% & ≥95%).

Model discrimination was assessed by calculating the Harrell's C-statistic and by visual inspection of Kaplan–Meier survival curves separation between five patient survival risk groups.[16] Model fit was assessed by calculating the prognostic index for individual patients in the temporal validation cohort and constructing a Cox-proportional hazards model to estimate the regression coefficient on the prognostic index.[15] Calibration was assessed by comparing predicted survival probability against actual survival in a Cox-Proportional Hazards model and by plotting Kaplan–Meier survival curves of observed versus predicted survival in 5-patient survival risk groups. Survival probabilities used to assess calibration were calculated using the baseline survival function and prognostic index derived from the base model in the model development cohort.

2.5 | Ethical approval

This study was conducted with approval of the Central Adelaide Local Health Network Human Research Ethics Committee (HREC/17/RAH/408).

All analyses were performed using Stata (Version 14.2, Stata Corp, TX, USA) using the somersd package[17] and R Statistical Software (Version 2022.01.01).

3 | RESULTS

3.1 | Patient cohort

There were 11 302 participants included for analysis. Among the total patient cohort, 6254 participants were included in the development cohort and 5048 participants were included in the validation cohort, Table 1.

In the model development cohort, most participants were male (62.8%) and Caucasian (79.2%). The most common primary kidney disease for participants was glomerulonephritis (45.6%) followed by polycystic kidney disease (13.5%). Participants most commonly had a body mass index within the normal range (40.4%) followed by 32.9% of participants being classified as overweight. Most patients had received kidney replacement therapy for at least 1–5 years prior to transplant (52.9%), Table 1.

Comorbid medical conditions were present in several participants with 16.1% having diabetes mellitus and 15.0% having ischaemic heart disease. Most participants had never been cigarette smokers (54.9%). Overwhelmingly, participants were receiving their first kidney transplant (86.2%) and the majority (76.9%) had low pre-transplant sensitisation with a peak panel reactive antibody less than 20%, Table 1.

3.2 | Development outcomes

The model development cohort was randomly split into derivation and validation cohorts stratified by age, ethnicity, diabetes status and deceased donor status (neurological determination of death or donation after circulatory death). There were 4209 participants included in the derivation cohort and 2045 participants in the validation cohort, Figure 1. No significant differences were observed between ethnicity, diabetes status, donor status, primary kidney disease, or transplant era between the cohorts.

On univariate analysis age, sex, BMI, ethnicity, primary kidney disease, presence of comorbid medical conditions (diabetes, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, and respiratory disease), smoking status, kidney replacement therapy duration, age, donor cause of death, donor hypertension, HLA mismatch, ischaemic time, donor type (medical or trauma), donor-recipient BMI mismatch and peak panel reactive antibody were significant at a p-value of 0.20. Non-significant factors were graft number, donor sex, donor ethnicity, donor diabetes status, donor status (neurological determination of death or donation after circulatory death) and transplant era. Linearity was assessed for all continuous variables. All included continuous variables were felt to be linearly related except kidney replacement therapy duration, body mass index and

TABLE 1 Baseline characteristics of 11 302 Australian kidney failure patients in receipt of a kidney transplant between 1st January 2000 and 31 December 2020 registered in the Australia New Zealand Dialysis & Transplant Registry (ANZDATA).

Factor	Development Cohort 2000–2014 Frequency (%) $N = 6254$	Validation Cohort 2015–2020 Frequency (%) $N = 5048$	p-Value[a]
Median age at transplant (IQR)	51 (40, 59)	54 (43, 62)	<.001
Gender (Male)	3929 (62.8)	3230 (64.0)	.21
Ethnicity			<.001
Caucasian	4951 (79.2)	2939 (58.2)	
Aboriginal and/or Torres Strait Islander	319 (5.1)	226 (4.5)	
Asian	685 (11.0)	692 (13.7)	
Other	299 (4.8)	1191 (23.6)	
Primary kidney disease			<.001
Glomerulonephritis	2854 (45.6)	1864 (36.9)	
Polycystic kidney disease	846 (13.5)	617 (12.2)	
Reflux nephropathy	543 (8.7)	295 (5.8)	
Hypertension	351 (5.6)	380 (7.5)	
Diabetes	667 (10.7)	937 (18.6)	
Other	993 (15.9)	955 (18.9)	
Body mass index[b]			<.001
Underweight (<18.5)	289 (4.6)	92 (1.8)	
Normal (18.5–24.9)	2365 (37.8)	1397 (27.7)	
Overweight (25–29.9)	1923 (30.7)	1593 (31.6)	
Obese (≥30)	1271 (20.3)	1417 (28.1)	
Not recorded	406 (6.5)	549 (10.9)	
Duration of kidney replacement therapy			<.001
0–0.49 years	162 (2.6)	312 (6.2)	
0.5–0.99 years	439 (7.0)	431 (8.5)	
1–5 years	3306 (52.9)	2953 (58.5)	
>5 years	2347 (37.5)	1352 (26.8)	
Smoking status			<.001
Never	3386 (54.9)	2931 (58.1)	
Former	2010 (32.6)	1653 (32.8)	
Current	775 (12.6)	464 (9.2)	
Comorbid medical conditions at kidney replacement therapy commencement			
Diabetes mellitus	1004 (16.1)	1385 (27.4)	<.001
Ischaemic heart disease	937 (15.0)	819 (16.2)	.06
Peripheral vascular disease	392 (6.3)	347 (6.9)	.18
Cerebrovascular disease	279 (4.5)	244 (4.8)	.34
Chronic respiratory disease	353 (5.6)	345 (6.8)	.01
Graft number			.13
1	5389 (86.2)	4403 (87.2)	
2	721 (11.5)	552 (10.9)	
3 or more	144 (2.3)	93 (1.8)	
Median donor age (IQR)	48 (32, 58)	49 (35, 60)	<.001
Donor sex (male)	3551 (56.8)	2892 (57.3)	.61
Donation after circulatory death donor status	888 (14.2)	1412 (28.0)	
Donor hypertension history	1414 (23.0)	1256 (24.9)	.01
Transplant era			NA

(Continues)

TABLE 1 (Continued)

Factor	Development Cohort 2000–2014 Frequency (%) $N = 6254$	Validation Cohort 2015–2020 Frequency (%) $N = 5048$	p-Value[a]
2015–2019	0 (0)	5048 (100)	
2010–2014	2789 (44.6)	0 (0)	
2005–2009	1820 (29.1)	0 (0)	
2000–2004	1645 (26.3)	0 (0)	
HLA mismatch categories[c]			.001
0–2	2089 (33.7)	1569 (31.1)	
3–4	1938 (31.2)	1526 (30.2)	
5–6	2179 (35.1)	1939 (38.4)	
Unrecorded	48 (0.8)	14 (0.3)	
Peak panel reactive antibody (%)			<.001
0–19	4694 (76.9)	3612 (71.6)	
20–49	595 (9.8)	362 (7.2)	
50–79	373 (6.1)	286 (5.7)	
80 or above	439 (7.2)	547 (10.8)	
Unrecorded	153 (2.4)	241 (4.8)	
Median total cold ischaemic time to nearest hour (IQR)	12 (10,15)	10 (7, 14)	<.001

[a]p-Value for difference between development and validation cohort. p-Value calculated using t-test for normally distributed continuous variables, Wilcoxon Rank Sum Test for non-normally distributed continuous variables and Chi-squared test for categorical variables.
[b]Body Mass Index—weight (kilograms) divided by the square of height (metres).
[c]Human Leukocyte Antigen mismatch categories—loci characterised at HLA-A, -B & -DR.

peak panel reactive antibody. These variables were reclassified as categorical variables. (Supplemental Table S1).

Variables were then assessed for inclusion in the final model using backwards selection. BMI was removed as it was not statistically significant in the univariate or multivariable model. All recipient comorbidities, except respiratory disease, were non-significant in the multivariable model however were highly significant on univariate analysis and were included in the final model due to their clinical significance. Transplant era & recipient-donor BMI were not significant on univariate & multivariate analysis so were not included in the final model. The proportional hazards assumption for all variables was tested with Schoenfeld residuals and no clear violation was present.

An interaction was observed between included co-morbid medical conditions. We tested the inclusion of an interaction term and a new categorical variable denoting number of co-morbid medical conditions. The models were compared using AIC and the base model without the interaction term was considered a better fit for the data with a lower AIC. We proceeded with the base model for our analysis.

The derivation and validation cohorts were compared using Harrell's C-statistic. The Harrell's C-statistic for the derivation cohort was 0.72 (95% confidence interval (CI) 0.70–0.74) and the validation cohort was 0.70 (95% CI 0.67–0.73). The dataset was combined, and the final multivariable model was applied to calculate the final point estimates, Table 2.

3.3 | Validation outcomes

The base model was validated with a temporal cohort of patients from the ANZDATA Registry. The temporal validation cohort included 5048 adult patients who had a kidney transplant between 2015 and 2020, Figure 1.

The base model demonstrated good discrimination in the temporal validation dataset with a Harrell's C-statistic of 0.72 (95% CI 0.69–0.75). The discrimination performance of the base model was further examined by plotting Kaplan–Meier survival curves for different survival risk groups, Figure 2. Kaplan–Meier survival curves were well separated between each risk group suggesting good discrimination performance of the model. Model calibration was tested by plotting Kaplan–Meier survival curves of predicted and actual patient survival, Figure 3. In patients with an estimated 5-year post-kidney transplant survival of 95% of above, 96.4% (95% CI 94.3%–97.7%) of these patients were alive at 5-years post-kidney transplant and for patients with an estimated 5-year post-kidney transplant survival of 80% or less, 71% (95% CI 62.9%–77.9%) of those patients were alive at 5-years post-kidney transplant.

Model fit was examined by including the patient's predicted survival probability as a single predictor variable against the outcome of actual patient survival in a Cox-proportional hazards model. The calculated coefficient for predicted patient survival was 0.93 (95% CI 0.77–1.10) suggesting good model fit. A perfectly fit model will have a

TABLE 2 Multivariable Cox proportional hazards model of patient survival post-kidney transplantation in 6254 Australian kidney transplant recipients between 1st January 2000 and 31st December 2014 registered in the Australia New Zealand Dialysis and Transplant Registry (ANZDATA).

		Hazard ratio	95% Confidence interval	*p*-Value
Age at transplant (years)		1.05	1.04–1.05	<.05
Gender	Female	Ref		
	Male	1.18	1.01–1.38	.035
Ethnicity	Caucasian	Ref		
	Aboriginal and/or Torres Strait Islander	2.14	1.62–2.81	<.05
	Asian	0.89	0.68–1.15	.37
	Other	0.97	0.64–1.47	.88
Primary kidney disease	Glomerulonephritis	Ref		
	Analgesic	2.72	1.49–3.48	<.05
	Polycystic kidney disease	1.09	0.88–1.36	.407
	Reflux nephropathy	0.89	0.64–1.23	.483
	Hypertension	1.15	0.85–1.55	.363
	Diabetes	1.30	0.94–1.79	.117
	Other	1.68	1.32–2.13	<.05
	Unknown	1.74	1.29–2.35	<.05
Comorbid medical conditions at kidney replacement therapy commencement	Diabetes mellitus	1.25	0.95–1.64	.113
	Ischaemic heart disease	1.05	0.86–1.27	.653
	Peripheral vascular disease	1.47	1.14–1.89	.002
	Cerebrovascular disease	1.23	0.93–1.64	.15
	Chronic respiratory disease	1.35	1.03–1.76	.029
Duration of kidney replacement therapy	<0.5 year	Ref		
	0.5–1 year	3.28	1.31–8.16	.01
	1–5 years	3.13	1.30–7.50	.01
	>5 years	3.56	1.48–8.57	.005
Smoking status	Never	Ref		
	Former	1.10	0.94–1.28	.229
	Current	1.54	1.26–1.88	<.05
Donor age (years)		1.00	1.00–1.01	.04
Donor status[a]	Trauma	Ref		
	Medical	1.05	0.88–1.25	.61
Donor hypertension		1.09	0.92–1.29	.34
HLA mismatch[b]		1.03	0.99–1.07	.12
Peak panel reactive antibody		1.01	1.00–1.01	<.05
Ischaemic time[c]		1.03	1.02–1.05	<.05

[a]Donor status—classification of trauma or medical cause of death.
[b]HLA mismatch—loci characterised at HLA-A, -B & -DR.
[c]Cold Ischaemic time—duration of time (h) from start of cold preservation to organ reperfusion.

co-efficient of 1. Rates of misspecification were low with only Aboriginal & Torres Strait Islander patients, patients with other as their primary kidney disease specification, ischaemic heart disease as a secondary medical condition and current smokers being significant on testing.

4 | DISCUSSION

We derived and validated a prediction model that model examines post-kidney transplant survival in kidney failure patients who have undergone kidney transplantation in Australia. The model uses readily

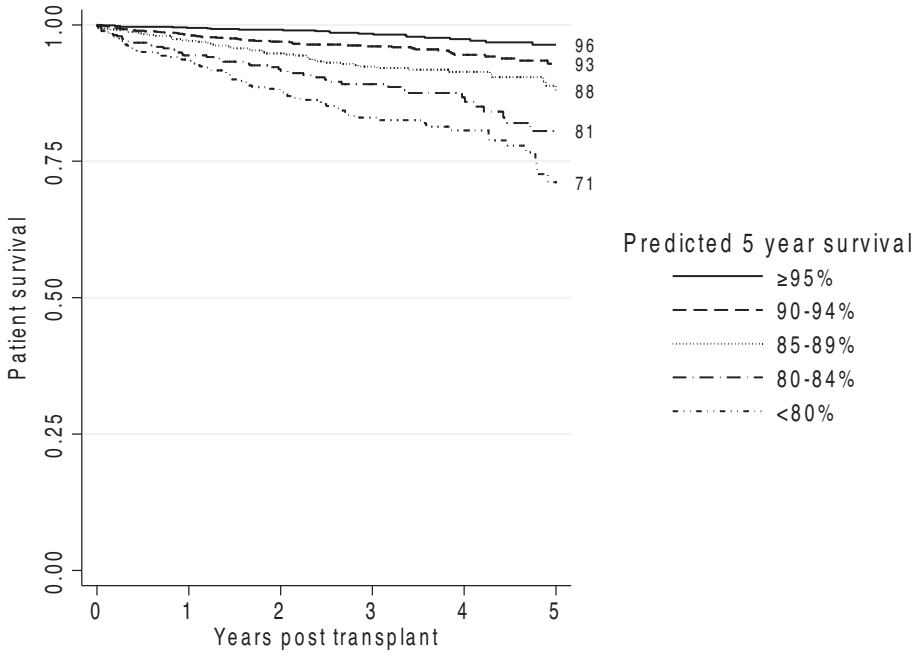

FIGURE 2 Kaplan–Meier survival curves of observed 5-year post-kidney transplant patient survival by predicted survival risk quintile examining base model discrimination performance in 5048 Australian kidney transplant recipients between 2015 and 2020.

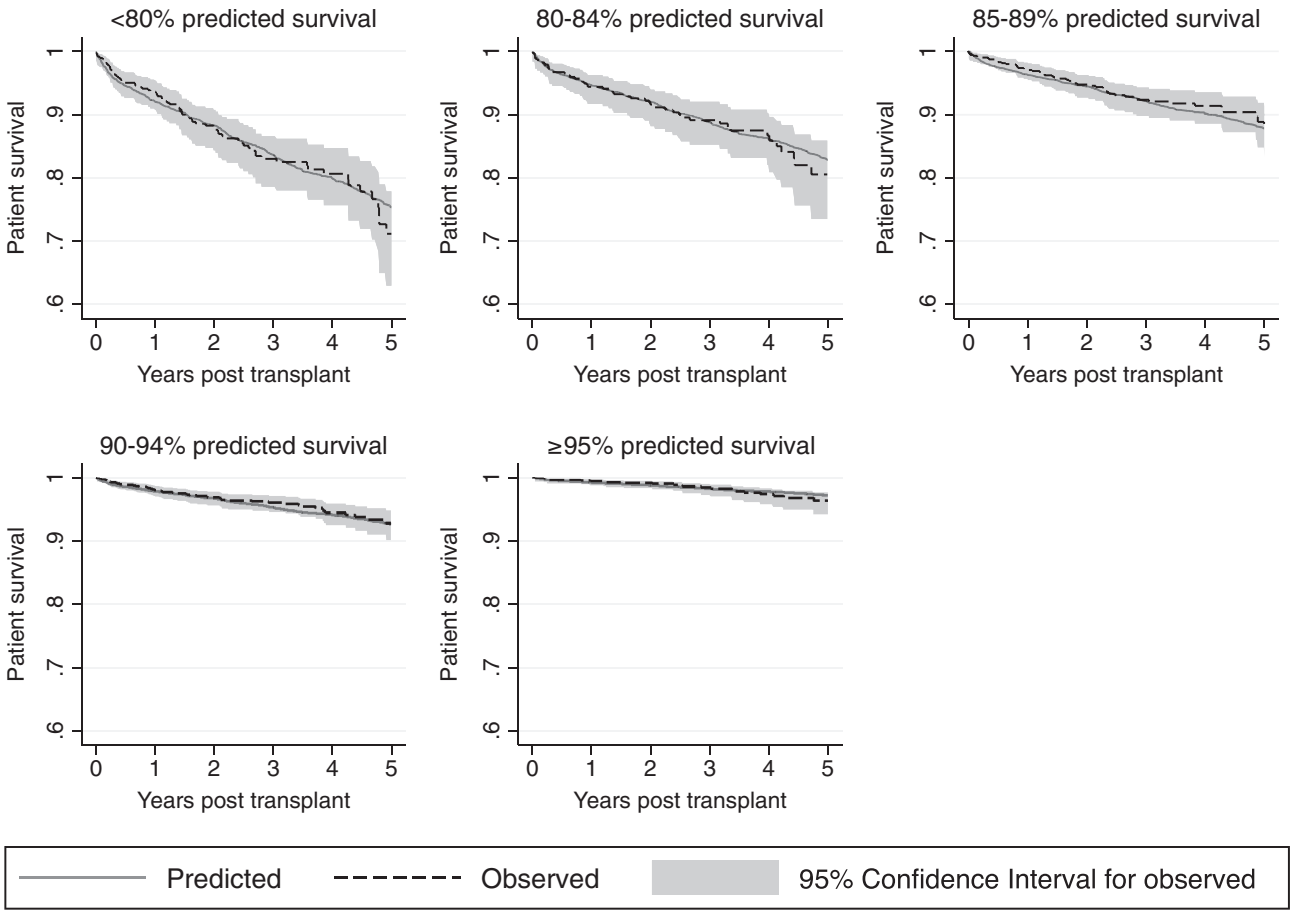

FIGURE 3 Calibration plots of observed patient survival compared to predicted 5-year post-kidney transplant patient survival by survival quintile in 5048 Australian kidney transplant recipients between 2015 and 2020.

available objective data that will assist estimations of patient survival and has several strengths including its use of Australian patient data, the complete capture of all kidney transplant recipients during the study period and the prediction performance of the model.

This prediction model allows estimates of post-kidney transplant survival to be calculated for patients with kidney failure. This information can be incorporated into assessments of patient suitability for kidney transplantation. Expected post-kidney transplant survival is an important aspect of determining eligibility for kidney transplantation and may be acting as an unmeasured confounder when comparing different rates of patient waitlisting and transplantation between different kidney transplant units. Using this survival model, researchers will be able to consider expected patient survival when assessing variations in access to kidney transplantation.

The model performed well when it was validated in the temporal patient cohort. Discrimination performance was satisfactory with a Harrel's C-statistic of 0.72 (95% CI 0.69–0.75). Clinically, this means that the model can predict which of two kidney failure patients will survive longer 72% of the time. The model was well calibrated with evidence of an excellent fit on calibration testing.[15] This indicates that the model can reasonably predict the expected survival for an individual kidney failure patient post-kidney transplantation. The satisfactory performance of this model will allow confident estimates of post-kidney transplant survival in Australia and will aid in assessing the suitability of kidney transplantation for patients with kidney failure.

Our analysis has highlighted known differences in demographics and long-term outcomes in Australia compared to other international transplant systems.[10,11] In our patient cohort, most patients had glomerulonephritis as their cause of kidney disease (36.9%) compared to 17.1% in the USA in 2020 and 24% of patients registered on the kidney transplant waiting list in the UK in 2021.[18,19] Rates of diabetic kidney disease were similar between the UK and Australia however 36.1% of all kidney transplant recipients had diabetes in the USA in 2020 compared to 18.6% in our validation cohort.[18] Duration of dialysis treatment prior to transplant also varied with 26.8% of Australian patients receiving 5 or more years of dialysis compared to 31.1% in the USA.[18] Australia also achieved lower median cold ischaemic times compared to the USA and UK.[11,19] These highlighted differences may influence post-kidney transplant survival and underline the importance of developing tailored models for use in Australia.

It is important to recognise that pre-existing survival models exist in the field of kidney transplantation.[9,20–23] These models all vary in their outcome measures, cohort characteristics, modelling methods and model performance. A large proportion of models investigate graft loss as their primary outcome rather than patient survival.[9] Whilst graft loss remains an important outcome post-transplantation, there are several factors that may influence graft loss, such as immunological & surgical factors, which would not be appropriate to apply when considering patient eligibility for kidney transplantation. For models that investigate factors related to patient survival post-transplant, many are based on analyses using patient data from the USA.[9] Some studies incorporate European patient data, and a very small pool of studies incorporate patient data from Oceania and Asia.[9] Given the demographic and healthcare system differences between these regions, models that use patient data from Australia are clearly needed, particularly if estimates generated from these models may be used to implement system wide policy change. Like our model, most models use Cox Proportional Hazards methods to estimate post-transplant survival. Unlike our model, most studies do not incorporate external or temporal validation. Discrimination performance for most models was below the performance of our model. In those models with superior discrimination performance, some included variables that would be difficult to incorporate prior to transplantation such as pulse-wave Doppler measurements, time-to-transplant or, 1-year post-transplant kidney function.[21,24–28] As opposed to previously published models, our model calculates survival estimates using Australian patient data and readily available co-variables. This differentiates it from previously published models and will ensure confident translation of its use for policy and system change in Australia.

One of the most common survival scores used in kidney transplantation is the Estimated-Post Transplant Score (EPTS).[22,29] The EPTS is primarily used in organ allocation and uses 4 variables (age, prior kidney transplant history, diabetes status and dialysis duration) to calculate a predicted patient survival score for the purposes of ranking patients for organ allocation. The EPTS was developed in the United States of America and was required to be easily calculated from objective, readily available variables so that it could be rapidly applied during the time pressured organ allocation process.[22] As such, only four variables were included. The EPTS score has been validated in Australia and performed moderately well in discriminating survival (C-statistic of 0.67).[29] The discrimination performance of the EPTS was lower compared to our model when applied to our patient cohort (C-statistic 0.67; 95% CI 0.65–0.69 in the development cohort and 0.70; 95% CI 0.67–0.72 in the temporal cohort). The inclusion of a limited number of variables in the EPTS limits its ability to characterise individual patient variation that may influence post-kidney transplant survival. Important factors, such as prior cardiac disease, are not included in the EPTS and many of these factors are known to remain strong drivers of outcomes post-transplantation.[30] For the purposes of assessing candidacy for kidney transplantation, using a survival model that incorporates a broader range of variables that may influence post-transplant survival is important to better characterise individual variation. Our model allow incorporates these additional variables without sacrificing model performance.

Our model has been developed from observational registry data and readers should consider the limitations of this data. Readers should consider the potential for residual confounding and misclassification of data. Our model only examines patients who were successful in being waitlisted for kidney transplantation. Successfully waitlisted patients complete a full transplant assessment and have therefore been identified as patients who are likely to benefit from

transplantation. This should be considered by the reader when applying this score beyond this population. A Cox proportional hazards model has also been used for survival prediction in this patient cohort which indirectly assesses baseline hazard distribution. A Cox model is advantageous when modelling relative effects but may have limitations when applying it to a new population. We plan future work using flexible parametric survival models.

In summary, our prediction model identifies and weights key parameters of prognostic importance in patients who are undergoing kidney transplantation in Australia. Our model will enable predictions of survival outcomes in patients at the time of transplantation and may have broader administrative applications in defining potential demand for kidney transplantation and better characterising differences in rates of waitlisting and transplantation across units in Australia.

AUTHOR CONTRIBUTIONS

Lachlan C. McMichael: Research design; manuscript preparation; statistical analysis. **Aarti Gulyani**: Statistical analysis. **Philip A. Clayton**: Research design; manuscript preparation; statistical analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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

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