Development and validation of a risk index to predict kidney graft survival: the Kidney Transplant Risk Index

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BACKGROUND

Transplanting kidneys to recipients based on the presumed longevity of the kidney graft is a strategy that is being tried to increase the kidney donor pool. For this graft failure risk prediction models are crucial in deciding who is the most suitable recipient. Our objective was to develop and validate statistical and machine learning predictive models to predict death-censored graft failure following deceased donor kidney transplant, using time-to-event (survival) data in a large national dataset from Australia.

Methods

Model development was a sequential process with the following five steps: data preparation, splitting the data set into training and validation datasets, variable selection, model training, and model evaluation (Figure 1).

Data preparation: Data included donor and recipient characteristics (n=98) of 7,365 deceased donor transplants from January 1st, 2007 to December 31st, 2017 conducted in Australia.

Splitting the data set into training and validation datasets: The models were trained using 70% of the data and validated using the rest of the data (30%).

Variable selection: Seven variable selection methods were used to identify the most important independent variables included in the model: *Expert opinion, Principal component analysis, Elastic net*

Model training: Predictive models were developed using: survival tree, random survival forest, survival support vector machine and Cox proportional regression.

Model evaluation: Model performance was evaluated using two metrics: discrimination and calibration.

- *Discrimination* : (1) The model with best discriminatory power, assessed using concordance index (C-index); (2). the indices of the best fitting models were categorized into four groups at the 16th, 50th and 84th centiles to develop four prognostic groups: Good, Fairly good, Fairly poor and Poor. The survival of these four groups were compared using Kaplan–Meier plots
- *Calibration:* Bootstrap resamples were used to estimate the bias-corrected predicted and observed mean survival at 3 and 5 years following transplantation. Perfect agreement between the predicted and observed mean survival indicates a perfectly calibrated prediction model

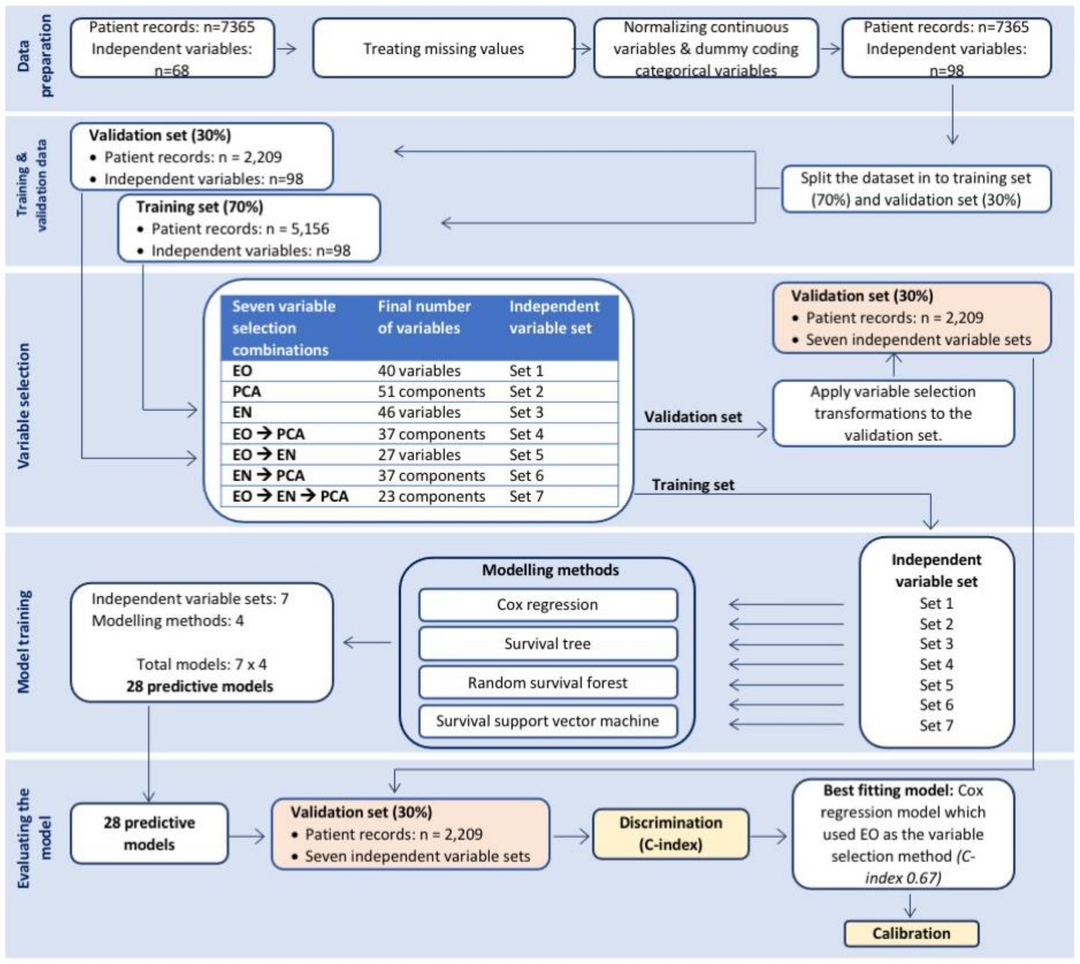

Figure 1 : Model development and validation workflow

EO: Expert opinion; PCA: Principal component analysis; EN: Elastic net

RESULTS

The median age of donors was 52 years (inter-quartile range 41 to 60) and of the recipients was 47 years (inter-quartile range 32 to 58). The majority were males (63%). About 87% of the grafts were primary grafts.

Table 1 : C-index of the seven different variable selection methods and four predictive models. *(More accurate models have a higher C-index. The joint two best indices are in bold)*

	Variable selection	Predictive models			
		Cox	RSF	SVM	DT
Combination 1	EO	**0.67**	0.66	0.58	0.60
Combination 2	PCA	0.65	0.60	0.65	0.55
Combination 3	EN	0.65	**0.67**	0.53	0.60
Combination 4	EO → PCA	0.61	0.62	0.52	0.57
Combination 5	EO → EN	0.66	0.61	0.61	0.57
Combination 6	EN → PCA	0.64	0.65	0.56	0.61
Combination 7	EO → EN → PCA	0.64	0.63	0.62	0.60

EO: Expert opinion; PCA : Principal component analysis; EN : Elastic net; RSF : Random Survival Forrest; SVM : Support Vector Machine; DT: Decision Tree

- Cox proportional regression and RSF outperformed the other two models.

Table 2 : Final set of independent variables in the best fitting Cox and RSF models

Model	Number final variables	Variable names
Cox	7	*Donor variables (n=2)*
		Donor age, Donor hypertension
		Recipient variables (n=5)
		Age at transplant, Peripheral vascular disease, Primary renal disease, Duration of peritoneal dialysis, Duration of haemodialysis
RSF	20	*Donor variables (n=10)*
		Donor age, DR locus 1, A locus 2, Height, Donor diabetes, Donor hypertension, Cause of death, Creatinine – terminal, Oliguria, Race
		Recipient variables (n=10)
		Age at transplant, HLA-DR mismatch, Pre-emptive transplant, Duration of peritoneal dialysis, Duration of haemodialysis, Primary renal disease, Smoking, Peripheral vascular disease, Age at starting renal replacement therapy, number of previous rejections

- The Cox model used 7 independent variables while the RSF used 20 variables (Table 2).
- Since the Cox model was able to produce the same discriminatory power with lower number of variables, it was considered as the best fitting model.

Risk prediction index = Exp[(0.18249x [(Donor age$^{\$}$ - 45)/5]) + (-0.52013 x [$\log_2$ Donor age$^{\$}$]) + (0.35782 x A$^{\#}$ Donor: Hypertension) + (-0.12367 x [(Recipient age$^{\$}$ - 50)/5]) + (0.34845 x A$^{\#}$ Recipient : Peripheral vascular disease) + (–0.41705 x A$^{\#}$ Primary Renal Disease: Polycystic Kidney Disease) + (–0.27885 x A$^{\#*}$ Total duration of peritoneal dialysis between 1 to 24 months) + (0.33516 x A$^{\#}$ Total duration of haemodialysis > 24 months)]

$^{\#}$ If the relevant *variables* are positive A =1 or else A = 0
$^{\$}$ In years
* If the recipient has never been on peritoneal dialysis or duration more than 24 months; A = 0
If the risk prediction indices of the two patients are 1.00 (patient 1) and 2.72 (patient 2), it indicates that patient 2 has a 172% increase graft failure hazard than patient 1.

Figure 2: Calculation of the risk index using the Cox model

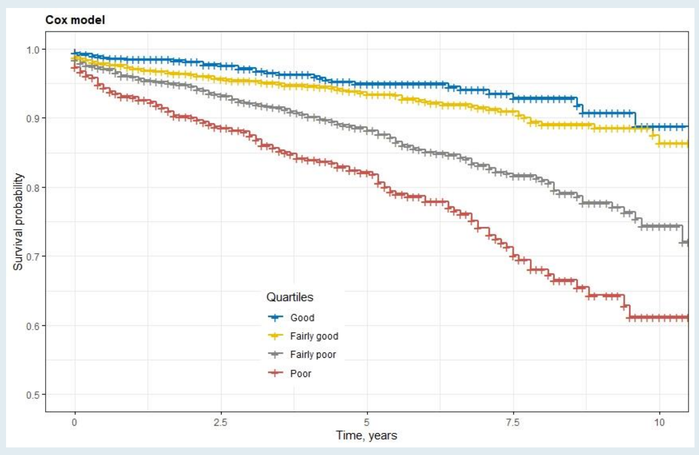

Figure 3: Kaplan–Meier survival curves indicating death-censored kidney graft failure by different risk prediction levels in the best fitting Cox model. The y-axis starts at a survival of 0.5 and not zero in order to more clearly show the separation between groups.

- As the risk groups move from "Good" to "Poor", the survival curves demonstrate a marked increasing risk of graft failure.

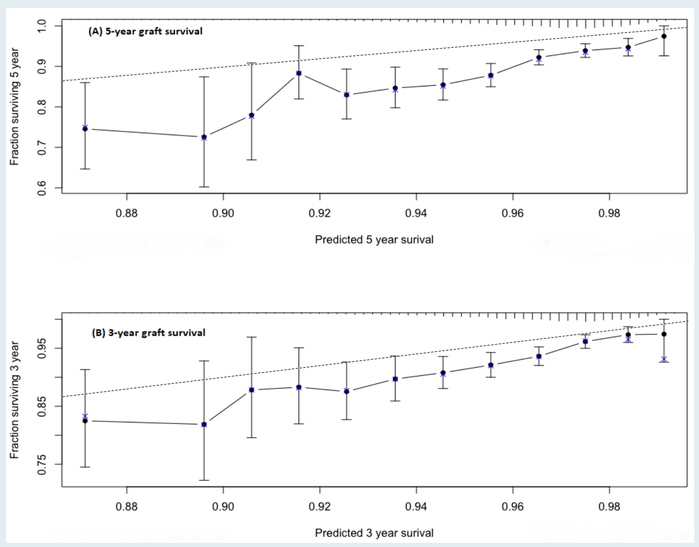

Figure 4 : Mean predicted survival (dashed line) versus the mean actual survival at 3 years and 5 years following transplantation

- The mean actual survival is consistently lower than the predicted survival at both 3 and 5 years.
- However, the gap between the prefect prediction line and the prediction line at both time periods reduces as the predicted survival increases.
- Overall, the Cox model shows moderate level of prediction accuracy.

CONCLUSION

This index displays sufficient robustness to be used in pre-transplant decision making and may perform better than currently available tools.

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