Trajectories of Systolic Blood Pressure Decline in Kidney Donors After Circulatory Death and Delayed Graft Function

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Research

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Abstract

Background: Kidneys donated after circulatory death (DCD) suffer a period of functional warm ischemia before death. This study aimed to assess the risk of delayed graft function (DGF) using patterns of trajectories of systolic blood pressure (BP) decline in DCD kidneys.

Methods: We studied all Australian DCD kidneys transplanted between 2014 - 2019, divided in a derivation (n=462, April 2014-January 2018) and validation (n=324, January 2018-December 2019) cohort, using latent class models and two-stage linear mixed-effect models.

Results: Eight different trajectories, with distinct patterns of systolic BP decline, were identified. Compared to recipients of donors with the fastest decline in systolic BP after withdrawal of cardio-respiratory support, the adjusted odds ratios (OR) (95%CI) for DGF in recipients who had received donors with the slowest systolic BP decline were 0.36 (0.16 – 0.80, random forest model) and 0.38 (0.17 – 0.86, least absolute shrinkage and selection operator models, LASSO), respectively. For every 1 mmHg per minute reduction in the rate of decline of systolic BP, the adjusted OR (95%CI) for DGF were 0.95 (0.91-0.99). Similar comparison was conducted in the validation cohort. Recipients who received donors with the slowest systolic BP decline from withdrawal of cardio-respiratory support till death did not experience an increased risk of DGF (Adjusted OR (95%): random forest: 1.01 (0.42-4.2) and LASSO: 1.17 (0.5-2.74)).

Conclusions: In DCD kidney donors, a slow decline in systolic BP during the agonal phase was not associated with adverse short-term outcomes after transplantation.

Introduction

The persistent shortfall in the availability of donor organ kidneys for transplantation has prompted the use of donation after circulatory death (DCD) donor kidneys. Since the introduction of the DCD program in 2006 in Australia, DCD donors represent the fastest growing form of organ donation, now constituting over 30% of all deceased kidney donors[1]. Similar patterns are observed worldwide. In the United Kingdom (UK), over 40% of all deceased donor kidney transplantation are from DCD donors[2]. While kidney transplantation from DCD in the United States (US) remains lower than other countries, there had been over a two-fold increase in the proportion of DCD kidney donors from 7.5–17% between 2005 and 2017[3].

Unlike donation after the neurological determination of death process, where the donor kidneys are well-oxygenated until the time of cold perfusion, DCD kidneys suffer a period of warm ischemia following withdrawal of circulatory support, which inevitably leads to early ischemic injury[4]. Despite being a valuable source of donor kidneys for transplantation with promising allograft survival rates (at least 75% graft survival rate at five years after transplantation), DCD kidneys remain under-utilised compared to donation after brain death donors (DBD). One of the key factors that determines organ procurement from DCD donors is the agonal time, defined as the period between withdrawal of life-sustaining treatment and circulatory arrest. For Maastricht category 3 kidney donors (controlled DCD donors), there are emerging data showing the duration of the agonal phase, combined with the haemodynamic changes and hypoxia during this critical phase are key predictors for adverse outcomes such as primary non-function and delayed graft function (DGF). A single study indicated an increase from 7 to 20 minutes with systolic blood pressure (BP) less than 80 mmHg doubled the risk of DGF, independent of the

duration of hypoxia[5]. Others have found that greater area under the curve of the systolic BP decline prior to circulatory arrest were predictive of DGF and early graft loss[6]. Many centres, therefore, have concerns of the potential ischaemic injury during the agonal phase, and donation is deemed unsuitable if cardiorespiratory arrest has not occurred within a certain timeframe of controlled withdrawal of life-supporting treatment. However, the evidence underpinning this specified duration is uncertain.

More importantly, progressive hemodynamic changes during the agonal phase may further influence the risk of DGF[7]. Continuous hemodynamic measures during the pre-donation period allows meticulous assessment of the relationship between dynamic changes of the systolic BP of the potential donors and DGF in transplant recipients. This study aimed to determine the association between trajectories of various patterns of systolic BP decline and DGF in a cohort of kidney transplant recipients of Maastricht category 3 kidney donors. Quantification of the variability of blood pressure changes during the agonal time on short-term graft outcomes will provide the necessary evidence to inform decision-making about donor suitability for transplantation.

Methods

This study was reported according to the STROBE guidelines for observational studies[8].

Study population (derivation cohort)

We included all actual DCD kidney donors that have been transplanted, and their corresponding recipients transplanted in Australia between 9th April 2014 and 2nd January 2018. The Electronic Donor Record (EDR) system was introduced in 2014, therefore details of the pre-donation hemodynamic records were not available prior to 2014. The EDR contains pre-, peri- and post-mortem information of all donors from each state/territory in Australia who were consented for organ donation in Australia and is managed and held by Australian Organ and Tissue Authority in Canberra, Australia. Multi-organ DCD transplants were excluded. Other data were sourced from Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry (recipient data and outcome measures). The institutional board and the human research ethics committee of the University of Western Australia approved the conduct of the study (ethics reference: RA/4/20/4743). Approval for data extraction from the EDR was granted by state and territory health departments and donor agencies. We have assigned this cohort as the derivation cohort because this dataset was provided to the investigator team during the first data request.

Data collection and linkage

Clinical data from the EDR includes hemodynamic parameters after WCRS such as systolic/diastolic BP (documented every 1-5 minutes using intra-arterial blood pressure monitoring, or in the absence of an arterial line, non-invasive oscillometric method (upper-arm cuff) was used), heart rate (documented every 10 minutes), prior requirement for inotropic/vasopressor support, the time to death, urine output over the 12 hours prior to death, cause of death and terminal serum creatinine. The EDR also contains the baseline characteristics of all actual deceased donors including age, sex, ethnicity, smoking history, personal history of diabetes, hypertension and body mass index (BMI). These data were entered into the EDR as part of routine data capture during the donation process by Donate Life Agency donor coordinator staff in each of the states and territories. The

average (standard deviation [SD]) number of repeated hemodynamic measures per donor across the cohort was 9.5 (5.6).

In Australia, absence of circulation is evidenced by absent arterial pulsatility for a minimum of 3 minutes and a maximum of 5 minutes, using intra-arterial pressure monitoring and confirmed by clinical examination

(absence of heart sounds and/or central pulses). In cases without an arterial line, electrical asystole is observed for a minimum of 3 minutes and a maximum of 5 minutes on the electrocardiogram and confirmed by clinical examination.

The ANZDATA Registry contains recipient data and includes records of all recipient baseline characteristics of age, sex, ethnicity, smoking status, diabetes, body mass index (BMI), transplanting state, primary cause of kidney failure, comorbidities such as chronic lung disease, history of hepatitis, prior cancer, vascular disease and time on dialysis before transplantation. Other transplant characteristics such as the transplant date, number of human leukocyte antigen (HLA) mismatches and total ischemic time were also recorded in the registry.

Data on DCD donors and the corresponding recipients were collated to allow for the alignment of the donor pre-, peri- and post-mortem events with other donor and recipient characteristics and outcomes measures using unique donor identifier. The de-identified dataset was prepared by ANZDATA registry and all linked data between the ANZDATA registry and the EDR (donors and recipients) were not re-identifiable. During the timeframe of this study period, machine perfusion was not used routinely across all states and jurisdictions in Australia.

Outcome measures

DGF was defined as recipients who required dialysis within the first seven days of transplantation.

Statistical analyses

Continuous variables were described using means (SD) and medians (interquartile range [IQR]). Categorial variables were summarised with counts and percentages.

Latent class mixed-effect model

We fitted a latent class mixed model to identify classes of systolic BP trajectories[9]. This approach assumed that the individual patterns of systolic BP decline during the agonal phase could be grouped into several patterns of systolic BP decline (latent classes), sharing similar tendency. Latent class analysis (LCA) is a modelling technique based on structural equation model, which aims to identify subgroups of individuals with “unmeasured” class memberships of similar clinical characteristics or outcomes that are not directly observable from the data[10]. The individual was assigned to a particular latent class membership with the highest probability of the outcome measure. When the measurement or outcome of interest is longitudinal, the formulation of the problem will become the identification of the subgroups of the developmental trajectories.

In our model, a two stage-approach was applied to link the latent class with the risk of DGF: in the first stage, the latent classes are estimated based on clinical characteristics; in the second stage, the estimated latent classes were used as predictors for clinical outcomes. The latent class model was fitted by considering time as a fixed effect and donor characteristics (including sex, age, donor body mass index, donor terminal creatinine, warm ischemia, donor causes of death) as random effects, with systolic BP as the response variable, and took the

form of a Gaussian distribution. In addition, the model was fitted with class-specific variance-covariance of the random-effects, with quadratic I-splines with 5 knots as link function to model the non-linear trend. Each trajectory was assigned to a certain latent class with the largest posterior likelihood. The number of latent classes was selected based on the Akaike information criterion (AIC), an estimator of in-sample prediction error, the entropy and by visual inspection of the patterns of trajectory decline in systolic BP[11].

Characterisation of latent classes and the association with DGF

The comparison of the donor profiles between the latent classes was conducted using one-way analysis of variance (ANOVA) and chi-square tests for continuous and categorical variables, respectively. The association between classes of trajectories of systolic BP decline and DGF was examined using a multivariable logistic regression and adjusted for selected donor and recipient characteristics, and the transplanting states. These variables were selected using two different approaches: Least absolute shrinkage and selection operator (LASSO)[12] and random forest[13].

Variable selection using LASSO and random forest

For LASSO, the penalisation parameter was chosen by cross-validation and the covariates with non-zero coefficient were included in the logistic regression, together with class, and fitted using maximum likelihood (that is, LASSO was used solely for variable selection). For the random forest model, we trained the model to predict DGF with 500 trees, using five randomly chosen variables at each split. We examined the rankings of variables importance in random forest model and selected the variables with the importance scores of greater than 10 to be included in the final logistic models together with systolic BP trajectory classes.

Effects of the slope and intercept of systolic BP decline on the risk of DGF

We fitted a two-stage model to assess the association between donor-derived systolic BP trajectories and its association with DGF.

Details of the two-stage model

SBP_{it} was denoted as the systolic BP (mmHg) for transplant i at time point t. First stage was written as $SBP_{it} = \beta_0 + b_{0i} + (\beta_1 + b_{1i})\, t + \epsilon_{it}$, where β_0 and β_1 were the fixed effect parameters, and b_{0i} and b_{1i} were the donor specific random effect intercept and slope, respectively using lmer function in R package lme4[14]. In the first stage, we used a linear mixed-effects model for systolic BP, with a random intercept and random effect for measurement time for each recipient. This longitudinal model allowed characterisation of individual systolic BP trajectories by the donor-specific intercept and rate of systolic BP decline (slope). We also tested the interaction between classes of systolic BP decline, donor age and DGF, and found donor age was not an effect modifier between the specific systolic BP latent classes and DGF.

In the next stage, the donor-specific intercept and rate of systolic BP decline were used in a multivariable logistic model for DGF, adjusted for other donor and recipient characteristics, and the transplanting states. These covariates were selected using similar methods to those described for the latent class approach (LASSO and random forest). The second stage model used the slope of systolic BP $\widehat{\mathrm{b}_{1\mathrm{i}}}$estimated from Stage 1. This was written as: $logit\left(P\left(DGF_i = 1\right)\right) = \alpha_0 + \alpha_1 \hat{b}_{1i} + \gamma^T x_i$, where $\alpha_1$was the coefficient for the estimated

slope of systolic BP; and $\mathbf{x_i}$ included the other variables in the multivariate logistic regression model. These variables were similar to those integrated in the latent class analyses and γ were the vectors of the logistic regression coefficients.

Classification DGF and model evaluation

We compared the additional performance gained from the latent class trajectories, slope and intercept of systolic BP in addition to traditional clinical variables using random forest modelling. Each model was evaluated using 5-fold cross validation and repeated by 50 times. The accuracy rate and the Area Under the Receiving Operator Curve (AUC-ROC) were used to evaluate the performance of the models.

Validation cohort

Validation of the findings from the derivation cohort (the 8 latent classes, slopes and intercept of systolic BP) was conducted using data from all Australian DCD donors between 6th January 2018 to 24th December 2019. This was made available to the investigators during the second data request.

Sensitivity analyses

Using similar modelling strategies of latent class modelling, variable selections using Random Forest and LASSO, logistic regression and model evaluation; we also assessed the association between trajectories of diastolic BP and DGF. Given the AIC and entropy with 8 and 9 latent classes were similar, we then evaluated the association between 9 different classes of systolic BP trajectories and DGF in the sensitivity analyses.

Results

Derivation cohort

Characteristics of the donors

A total of 472 actual DCD kidney donors between January 2014 and January 2018 was available for analysis. We included 462 in the latent class analyses, after excluding 10 donors with one haemodynamic entry (**Figure 1**). Most donors were male (62.8%), with a mean (SD) age of 47.6 (16.4) years. The mean (SD) terminal serum creatinine was 101 (107.6) μmol/L, and the average (SD) duration of withdrawal of cardio-respiratory support (WCRS) was 22.3 (15.7) minutes. Approximately 50% required inotropic support prior to WCRS and only 5.7% experienced oliguria in the preceding 24 hours prior to the declaration of death. The most common causes of death were cerebral hypoxia (39.2%), followed by intracranial bleed (24.5%) and traumatic brain injury (16.9%) (Table 1).

*Characteristics of kidney transplant recipients (*Table 2*)*

A total of 696 transplant recipients (from 379 donors) were included, and 380 (54.6%) had DGF. Approximately 60% of the recipients were men, most (70%) were European Australians. The major primary causes of kidney failure were glomerulonephritis, followed by diabetes mellitus and polycystic kidney disease. Around 20% had prevalent vascular disease at the time of transplantation.

Characteristics of the various patterns of trajectories of systolic BP decline

The maximum number of patterns examined was eleven and the number of patterns that best captured the trajectories of systolic BP decline was identified as eight (**Supplementary Figure 1**). The characteristics of the eight patterns are shown in Table 1 and **Figure 2**. There were significant differences in the WCRS times, intercept and slope of systolic BP decline, donor age, use of inotropic support during the pre-terminal phases, presence of oliguria in the last 12 hours preceding death, total ischemic time, and the causes of death between these classes of systolic BP decline. Donors that belonged to trajectory class 8 had the longest WCRS time (mean (SD): 60 (23) mins) and the slowest decline in systolic BP (-1.6 (0.9) mmHg/min), whereas those that were assigned to class one had the shortest WCRS duration (12 (3) mins) and a steep systolic BP decline (- 13.9 (2.8) mmHg)

Variables of importance

Variables selected for DGF using Random Forest included donor age, donor BMI, terminal serum creatinine, primary causes of kidney failure, diabetic status of the recipients, dialysis vintage, number of HLA mismatches, warm ischaemic time and the transplanting states (**Figure 3**). For LASSO, the key variables were donor age, sex, donor BMI, terminal serum creatinine, presence of oliguria within the past 12 hours prior to death, recipient age at transplantation, primary cause of kidney failure, diabetic status, dialysis vintage and the transplanting states (**Figure 4**).

Association between the patterns of trajectories of systolic BP decline and DGF

Compared to recipients of donors that belonged to latest class one (donors with the shortest WCRS time till death and the fastest decline in systolic BP), the odds of experiencing DGF in recipients of donors from all other patterns were similar, except for latent class 8 (donors with the longest WCRS duration till death). After adjusting for the variables selected using Random Forest and LASSO, the adjusted odds ratios (OR) (95%CI) for DGF were 0.36 (0.16 – 0.8) and 0.38 (0.17 – 0.86), respectively for recipients of donors from latent class 8 (**Figure 5**).

Association between the slope, intercept and DGF

We then explored the association between individual components of the systolic BP trajectories (slope of systolic BP decline and the intercept systolic BP at the time of withdrawal of cardio-respiratory support) and DGF, adjusting for the same variables selected by the Random Forest and LASSO in the multivariable logistic model. For every 1 mmHg per minute reduction in the rate of decline of systolic BP, the odds of DGF were reduced by 5% [adjusted OR (95%CI): Random Forest and LASSO: 0.95 (0.91-0.99)] (**Figure 6 and Supplementary Figure 2**). However, we did not observe an association between the initial systolic BP (the random intercept) and DGF [adjusted OR (95%CI): 1 (0.99 – 1.01)

Performance of the classification models for DGF

The model that included the slope of systolic BP decline had the highest accuracy rate of the cross validation with an average of 65.2% (for Random Forest selected variables) and 64.7% (for LASSO selected variables) compared to the models that included only clinical variables (65.0% and 64.1%) (**Figure 7**). The AUC-ROC for the

models that included the slope was 0.72 (0.68-0.76), while AUC-ROC for the models that included only the clinical variables was 0.7 (0.66-0.74).

Sensitivity analyses

A total of 6 different classes of diastolic BP trajectories were identified using latent class modelling (**Supplementary Figure 3**). The factors for defining these separate classes were intercept of the diastolic BP (initial diastolic BP at the time of WCRS), slope of diastolic BP decline and duration of withdrawal of cardio-respiratory support. There was no association between the various trajectories of diastolic BP decline and DGF, adjusted for variables selected by both LASSO and Random Forest (**Supplementary Figure 4**).

A total of 9 different classes of systolic BP trajectories were identified using latent class modelling (**Supplementary figure 5**). Compared to recipients of the donors with a fast decline in systolic BP (class 1), the adjusted odds (95%CI) of experiencing DGF in recipients of donors with the slowest systolic BP decline and the longest time from WCRS (class 8) were [Random Forest: 0.33 (0.14, 0.77)) and LASSO: 0.37 (0.16 – 0.86)] (**Supplementary figure 6**)

Validation Cohort

The cohort flow of the validation cohort is shown in **Supplementary Figure 7**. The baseline characteristics of the donors and recipients are shown in **Supplementary Tables 1 and 2**. Comparable findings were observed in validation cohort (324 actual donors were included in the latent class model and 272 donors (489 recipients) in the mixed effects model (**Supplementary Table 3**). We applied the 8 classes of systolic BP trajectories derived from the derivation cohort and tested them in the validation cohorts. (**Supplementary Figure 8**). Compared to recipients of donors with the shortest time from WCRS till death and fastest decline in systolic BP, the adjusted OR (95%) for DGF in recipients of donors with the longest WCRS and slowest systolic BP decline were [random forest: 1.01 (0.42-4.2) and LASSO: 1.17 (0.5-2.74)] (**Supplementary Figure 9**). For every 1 mmHg per minute reduction in the rate of decline of systolic BP, the adjusted ORs (95%CI) for DGF were [LASSO: 0.99 (0.94-1.0) and Random Forest: 0.97 (0.92-1.0)] (**Figure 6, Supplementary Tables 4 and 5**). The accuracy rate for the validation cohort of the classification models trained on derivation cohort is 59.6% (for Random Forest selected variables) and 60.7% (for LASSO selected variables) for the model that included the slope of systolic BP decline, indicating moderate discriminative ability, compared to the models that included only clinical variables (60.4% and 59.6%).

Discussion

Main findings

Using large development and validation datasets of recipients who have received DCD kidneys in Australia, we have shown that the slope of systolic BP decline and random intercept (initial systolic BP at the time of WCRS) are key factors that define the patterns of systolic BP decline during the agonal phase in our derivation and validation cohorts. For every 1 mmHg per minute reduction in the rate of decline of systolic BP, there was approximately a 1-5% reduction in the risk of DGF, but improvement in model performance was only modest with inclusion of the slope of systolic BP decline compared to using clinical variables alone. A longer agonal time was not associated with increased risk of DGF compared to donors with shorter agonal time, in both the

derivation and validation cohorts. Our research extends current knowledge by evaluating not only the duration of the agonal phase and blood pressure thresholds in isolation, but also the overall pattern and archetype of the rates of blood pressure decline over time in DCD donors using advanced statistical modelling techniques. This finding has provided the necessary evidence to safely extend and standardise the accepted agonal time to at least 90 minutes for DCD donors.

Comparison To Previous Studies

This novel finding differs from previous investigations, which reported a longer duration of functional warm ischemia, defined as the first recorded time of systolic BP less than 50 mmHg to cold perfusion, was associated with slow graft function, and premature graft loss in DCD kidneys[15]. Prior work have indicated that a longer agonal time was associated with a significantly increased risk of DGF and primary non-function by 50%[16], particularly in donors where the duration of systolic BP less than 80 mmHg exceeded 20 minutes before cold perfusion, with this effect more apparent in younger donors (aged < 40 years)[5]. However, there was no consistent relationship between the duration of hypotension in the agonal phase and allograft failure.

The explanation behind the discordance with our findings may be explained by rapidity of the blood pressure decline on the severity of ischemic-reperfusion injury (IRI) of the donor graft[17]. Ischemia, resulting from the extremes of hemodynamic changes in the deceased donor during the pre-donation phase, may lead to injury of the renal tubular, epithelial and endothelial cells[18]. This process can then initiate cytokine/chemokine release and recruits immune cells, including neutrophils, monocytes/macrophages and natural killer T cells, contributing to inflammatory responses and subsequent damage to the allograft[18]. The relationship between hypotension and the risk of acute kidney injury is also well documented in animal studies. Experimental work has shown that under normal physiological conditions, glomerular filtration rate (GFR) and renal blood flow are adequately autoregulated over a wide range of systolic BP. However, if systolic BP falls below the lower thresholds of 60-70 mmHg, renal blood flow auto-regulation will be lost, causing stimulation of the renin-angiotensin-aldosterone system, promoting renin release from granular cells of the renal juxtaglomerular apparatus to maintain perfusion pressure[19]. In the context of rapid blood pressure lowering, severe dysfunction of autoregulation of the afferent renal arterioles will occur, contributing to significant glomerular injury through reduction of renal blood flow to the compromised kidneys[20]. It is important to emphasize that even though autoregulation of renal blood flow is maintained during periods of systemic hypotension, intra-glomerular pressures of DCD donors are unpredictable during prolonged periods of severe hypotension, particularly among those that required inotropic support[21]. Other methodological differences which may explain the discrepant results between our study and prior research include dissimilar modelling approaches, characteristics of our study cohort and our sample size was very large in comparison to previous research.

Implications For Practice

Our study findings have important clinical implications. Currently, the duration of functional warm ischemic time for the kidneys is highly variable between countries, without robust evidence to support guideline recommendations. In the UK, organ retrieval will not occur if the time interval from the onset of functional warm ischemia is greater than 120 minutes[22]. In Spain and Belgium, the donation sector would accept a withdrawal of

cardio-respiratory support time of up to 2 hours before abandoning the process of donation[23]. In Australia, the time varies between 60-90 minutes, depending on the state jurisdiction[22]. Many of the DCD donors (approximately 40%) do not proceed to donation because they do not die within an acceptable timeframe after withdrawal of life support[24]. We have challenged the current belief and have shown that an extended duration of warm ischemia (at least up to 90 minutes) may not necessarily be harmful to the donor grafts, provided the decline in the blood pressure parameters is gradual over time. These data are important because it has unmasked potential opportunities to increase the donor pool of DCD kidneys by reducing discard rates, which are approximately 5-8% in Australia, but up to 15% in the US.

Strengths And Limitations

This study has some strengths. It is one of the largest cohorts of DCD donors with near complete repeated measures of hemodynamic parameters during the pre-donation phase. Unlike other registries, reporting and recording of details of the blood pressure decline of the donor organs are mandatory for all states and territory in Australia. Therefore, the current findings are reflective and generalizable to a diverse range of DCD kidneys. Using innovative, rigorous machine learning techniques and statistical modelling, we were able to define, for the first time, the various trajectories of systolic BP decline during the agonal phase of a national cohort of DCD donors. We have conducted extensive sensitivity analyses using different machine learning strategies for variable selections and our results are robust against a range of potential confounders, different classes of systolic BP trajectories, and the findings are consistent also for diastolic BP trajectories,

This study has some potential limitations. Longitudinal data on oxygen saturation concentrations in our donors was not available, so we were unable to examine the influence of hypoxia on DGF in the modelling. Confounding from unmeasured factors may also exist. We have only included those kidney donors that have progressed to donation and transplantation in the analyses and were unable to perform a direct comparison to donors that have not progressed, or non-utilised. We also do not have details of the second warm ischemia and duration of the anastomotic time from the ANZDATA Registry. Machine perfusion, unlike other countries, is not routine practice in Australia. Given the relatively short follow-up times, we did not have sufficient power and events to assess for medium and long-term graft survival. Future studies to examine the causal effects of pre-donation hemodynamic changes, DGF and graft survival are warranted.

Conclusions

In conclusion, we have defined the distinct and unique classes of systolic BP trajectories of DCD kidneys during the agonal phase, and the group membership, determined by the initial and rate of systolic BP decline from the time of withdrawal of circulatory support in both the derivation and validation cohorts. Notwithstanding potential injurious effects of prolonged functional warm ischemia prior to perfusion, we have shown that a slower decline in systolic BP during the agonal phase may not be harmful to the allograft in the short-term. It is therefore conceivable that the maximum allowable duration of agonal phase could be extended safely in the event of gradual donor systolic BP decline without necessarily compromising short-term allograft outcome.

Abbreviations

DGF
delayed graft function
DCD
donors after circulatory death
EDR
electronic donor record
ANZDATA
Australia and New Zealand Dialysis and Transplant Registry
AUC-ROC
Area Under the Receiving Operator Curve
LASSO
Least absolute shrinkage and selection operator
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement:guidelines for reporting observational studies

Declarations

Ethics approval and consent to participate

The institutional board and the human research ethics committee of the University of Western Australia approved the conduct of the study (ethics reference: RA/4/20/4743). Approval for data extraction from the EDR was granted by state and territory health departments and donor agencies.

Consent for publication

This manuscript does not contain any individual's patient data of any form.

Author contributions:

GW, YL, and WL conceived the study.

GW and YL wrote the manuscript.

YL performed the data analyses under the supervision of ATP, GW and JY.

GW, YL and WL have access to the datasets.

All authors contributed to the study design, edited the manuscript and advised on the presentation of results.

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Availability of data and materials

The authors are willing to share the statistical codes and program upon requests.

Conflict of interests

None declared for all authors.

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Tables

Table 1
Donor characteristics and characteristics of ten latent classes of systolic blood pressure trajectories of the derivation cohort

	All (N=462)	Class 1 (N = 70, 15%)	Class 2 (N =10, 2%)	Class 3 (N = 31, 7%)	Class 4 (N = 21, 5%)	Class 5 (N = 111, 24%)	Class 6 (N = 143, 31%)	Class 7 (N = 40, 9%)	Class 8 (N = 36, 8%)	p-values
Demographics										
Age (y, SD)	47.6 (16.4)	46 (15)	55 (11)	47 (17)	48 (16)	49 (16)	47 (16)	43 (21)	49 (17)	0.046
BMI (kg/m², SD)	27.8 (7.2)	29 (7)	26 (2)	28 (6)	26 (5)	29 (7)	28 (8)	26 (6)	26 (8)	0.112
Female (n, %)	172 (37.2)	13 (19)	6 (60)	11 (35)	7 (33)	44 (40)	64 (45)	15 (38)	12 (33)	0.189
Comorbidities (n, %)										
Hypertension	125 (27.1)	20 (29)	4 (40)	8 (26)	7 (33)	30 (27)	38 (27)	8 (20)	10 (28)	0.291
Smoking	168 (36.4)	27 (39)	5 (50)	9 (29)	9 (43)	43 (39)	47 (33)	14 (35)	14 (39)	0.689
Terminal creatinine (µmol/L, SD)	101.1 (107.6)	124 (126)	117 (203)	69 (29)	95 (137)	93 (87)	108 (124)	77 (50)	108 (84)	0.101
WCRS duration (min, SD)	22.3 (15.7)	12 (3)	36 (6)	18 (3)	48 (16)	18 (4)	17 (5)	23 (7)	60 (23)	<0.001
Intercept of SBP (mmHg, SD)	127.3 (40.5)	132 (39)	204 (26)	189 (29)	168 (24)	146 (21)	99 (24)	87 (26)	118 (23)	<0.001
Slope of SBP (mmHg, SD)	-7.8 (4)	-13.9 (2.8)	- 5.6 (0.9)	-12.3 (1.2)	-2.9 (0.6)	- 9.0 (1.2)	-6.6 (1.5)	-3.7 (0.9)	- 1.6 (0.6)	<0.001
Inotrope support (n, %)	224 (48.5)	24 (34)	6 (60)	8 (26)	4 (19)	46 (41)	94 (66)	25 (62)	17 (47)	0.001
Oliguria in last 12 h (n.%)	26 (5.7)	2 (2.9)	0 (0)	0 (0)	0 (0)	1 (0.9)	16 (11)	4 (10)	3 (8.6)	<0.001
Cold ischemic time (min, SD)	12.1 (3.5)	20.3 (73.8)	7.8 (2.7)	10.5 (3.7)	10.4 (2.5)	15.8 (59.0)	10.1 (3.5)	10.2 (3.9)	11.6 (4.5)	< 0.001
Causes of death (n, %)										< 0.001
Cerebral hypoxia	181 (39.2)	35 (50)	5 (50)	11 (35)	7 (33)	44 (40)	51 (36)	13 (32)	15 (42)	

*****WCRS - withdrawal from cardio-respiratory support, SBP- systolic blood pressure*

	All (N=462)	Class 1 (N = 70, 15%)	Class 2 (N =10, 2%)	Class 3 (N = 31, 7%)	Class 4 (N = 21, 5%)	Class 5 (N = 111, 24%)	Class 6 (N = 143, 31%)	Class 7 (N = 40, 9%)	Class 8 (N = 36, 8%)	p-values
Cerebral infarct	40 (8.7)	6 (8.6)	0 (0)	6 (19)	1 (4.8)	7 (6.3)	15 (10)	2 (5)	3 (8.3)	
Intracranial bleed	113 (24.5)	9 (13)	5 (50)	9 (29)	7 (33)	34 (31)	34 (24)	11 (28)	4 (11)	
Non-neurological	38 (8.2)	7 (10)	0 (0)	0 (0)	1 (4.8)	4 (3.6)	14 (9.8)	6 (15)	6 917)	
Others	12 (2.6)	0 (0)	0 (0)	0 (0)	1 (4.8)	3 (2.7)	7 (4.9)	0 (0)	1 (2.8)	
Traumatic brain injury	78 (16.9)	13 (19)	0 (0)	5 (16)	4 (19)	19 (17)	22 (15)	8 (20)	7 (19)	

***WCRS - withdrawal from cardio-respiratory support, SBP- systolic blood pressure*

Table 2
Characteristics of kidney transplant recipients of the derivation cohort

		All (n=696)	DGF (n=380)	No DGF (n=316)	P values
Age (mean, SD)		51.9 (13.4)	53.3 (12.3)	50.3 (14.5)	0.009
Induction therapy (n, %)		647 (93)	359 (94.5)	288 (91.1)	0.118
Sex (n, %)	Female	251 (36.1)	128 (33.7)	123 (38.9)	0.176
Ethnicity (n.%)	Asian	112 (16.1)	62 (16.3)	50 (15.8)	0.989
	Caucasian	495 (71.1)	269 (70.8)	226 (71.5)	
	Māori	11 (1.6)	7 (1.8)	4 (1.3)	
	Not reported	12 (1.7)	7 (1.8)	5 (1.6)	
	Other	56 (8)	30 (7.9)	26 (8.2)	
	Pacific Islanders	10 (1.4)	5 (1.3)	5 (1.6)	
Primary renal disease (n, %)	Diabetic Nephropathy	116 (16.7)	75 (19.7)	41 (13)	0.253
	Glomerulonephritis	268 (38.5)	142 (37.4)	126 (39.9)	
	Hypertension	50 (7.2)	29 (7.6)	21 (6.6)	
	Other	89 (12.8)	44 (11.6)	45 (14.2)	
	PCKD	103 (14.8)	55 (14.5)	48 (15.2)	
	Reflux Nephropathy	40 (5.7)	18 (4.7)	22 (7)	
	Uncertain	30 (4.3)	17 (4.5)	13 (4.1)	
State of transplant (n, %)	NSW	222 (31.9)	114 (30)	108 (34.2)	<0.001
	QLD	118 (17)	45 (11.8)	73 (23.1)	
	SA	39 (5.6)	20 (5.3)	19 (6)	
	VIC	292 (42)	194 (51.1)	98 (31)	
	WA	25 (3.6)	7 (1.8)	18 (5.7)	
Diabetic status (n, %)	Type 1 - Insulin Dependent	17 (2.4)	11 (2.9)	6 (1.9)	0.009
	Type 2 - Insulin Requiring	72 (10.3)	45 (11.8)	27 (8.5)	

		All (n=696)	DGF (n=380)	No DGF (n=316)	P values
	Type 2 - Non-Insulin Requiring	85 (12.2)	58 (15.3)	27 (8.5)	
Coronary artery disease	S	23 (3.3)	10 (2.6)	13 (4.1)	0.143
(n, %)	Y	132 (19)	81 (21.3)	51 (16.1)	
Cerebrovascular disease	S	9 (1.3)	5 (1.3)	4 (1.3)	0.725
(n, %)	Y	43 (6.2)	26 (6.8)	17 (5.4)	
Peripheral vascular disease	S	28 (4)	15 (3.9)	13 (4.1)	0.03
(n, %)	Y	51 (7.3)	37 (9.7)	14 (4.4)	
HLA mismatch	0	23 (3.3)	13 (3.4)	10 (3.2)	0.294
(n, %)	1	51 (7.3)	30 (7.9)	21 (6.6)	
	2	131 (18.8)	58 (15.3)	73 (23.1)	
	3	87 (12.5)	50 (13.2)	37 (11.7)	
	4	118 (17)	69 (18.2)	49 (15.5)	
	5	175 (25.1)	97 (25.5)	78 (24.7)	
	6	111 (15.9)	63 (16.6)	48 (15.2)	

Y – confirmed, S – suspected, PCKD – polycystic kidney disease

Figures

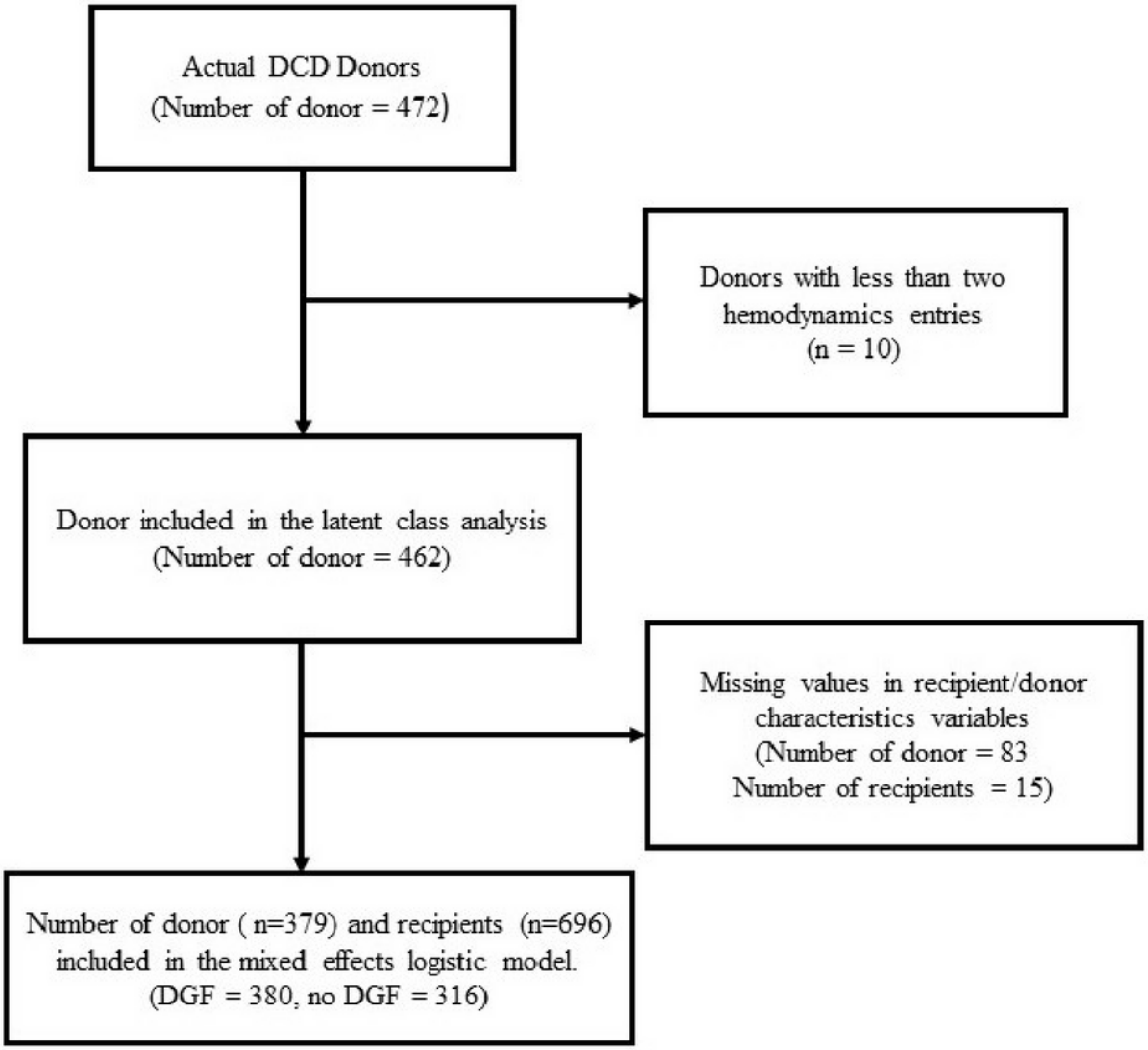


Figure 1

Cohort flow of DCD donors of the derivation cohort

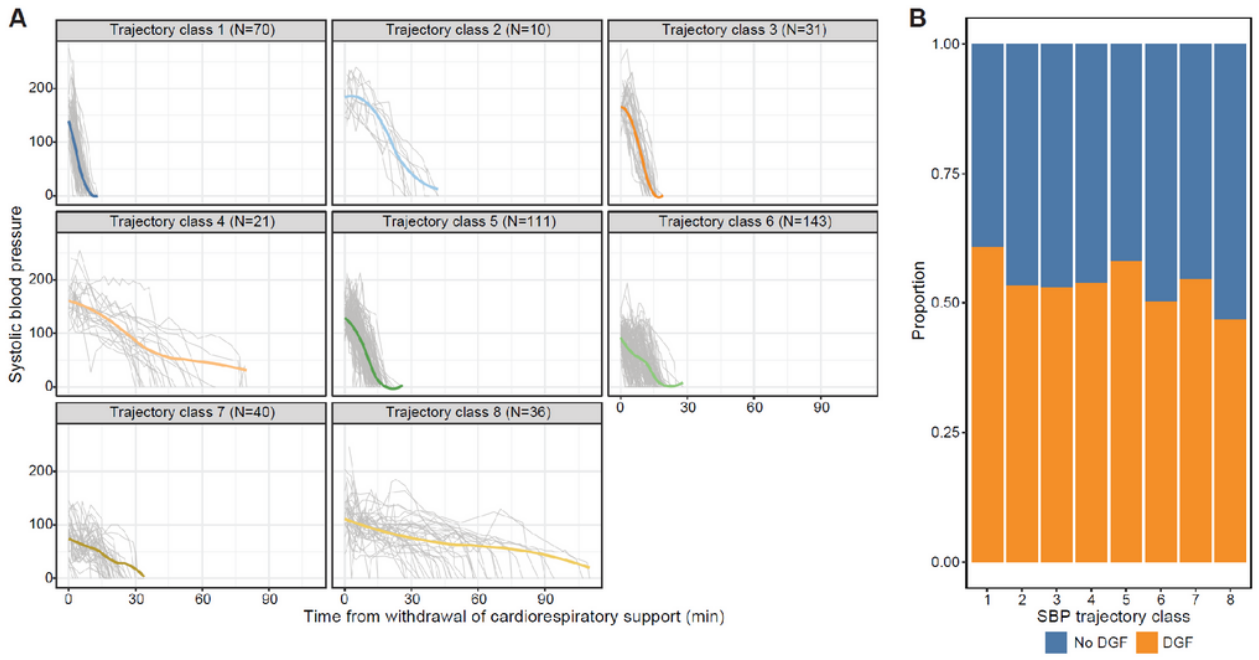


Figure 2

Latent classes of the trajectories of systolic BP decline and the proportion of DGF defined for each class (Derivation cohort)

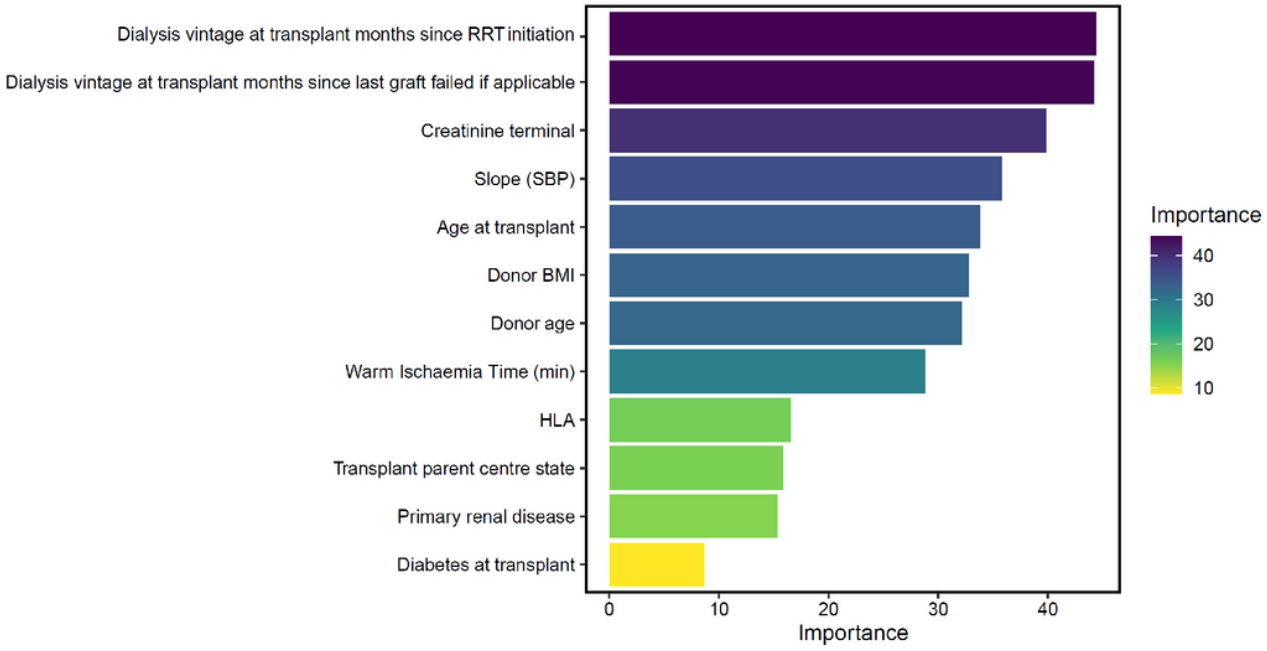


Figure 3

Variables of importance selected by Random Forest (Derivation cohort)

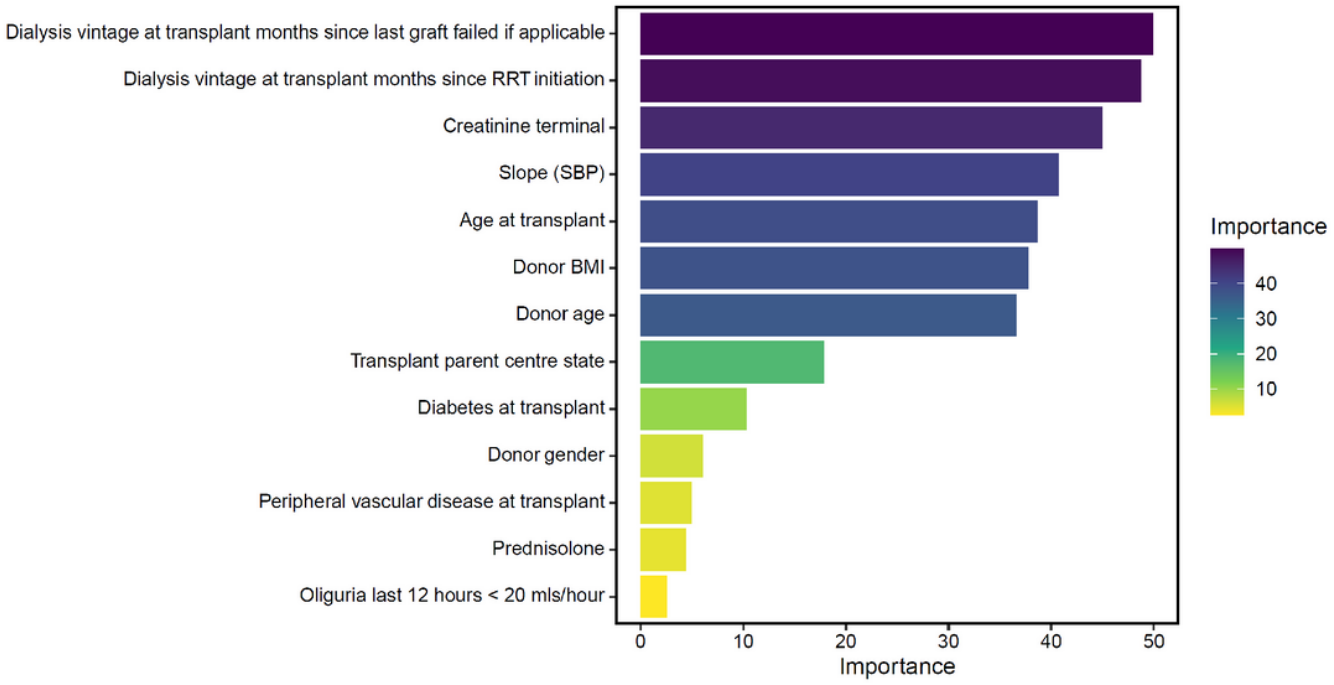
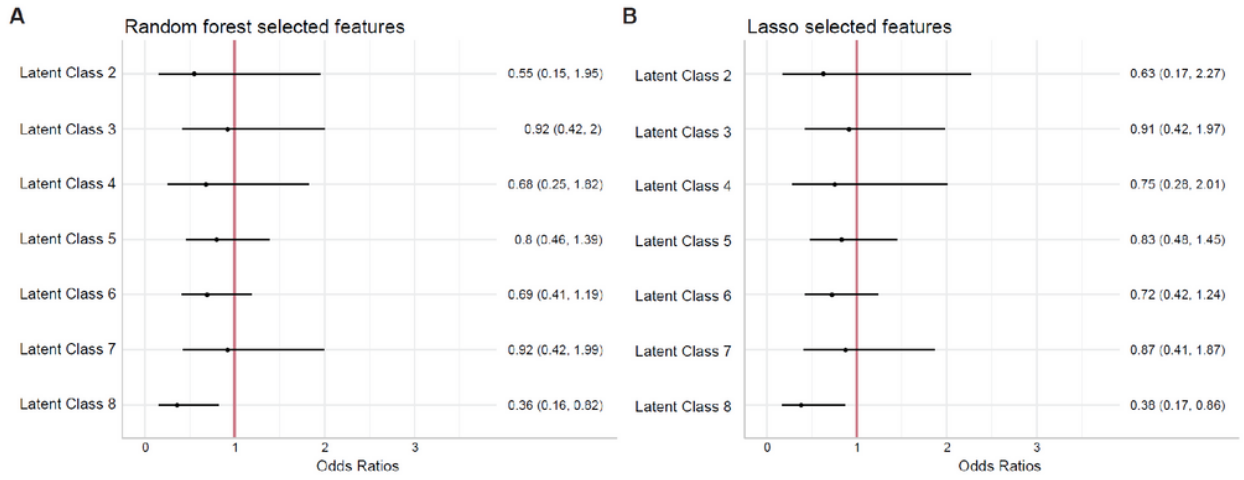


Figure 4

Variables of importance selected by LASSO (Derivation cohort)



**each of these classes of SBP trajectories were considered as separate exposures in 9 different models with the reference being class 1, adjusted for key variables donor age, donor body mass index, terminal serum creatinine, primary causes of kidney failure, diabetic status of the recipients, dialysis vintage, number of HLA mismatches, total warm ischaemic time and the transplanting states in the random forest selected features and donor age, sex, body mass index, terminal serum creatinine, presence of oliguria within the past 12 hours prior to death, recipient age at transplantation, primary renal disease, diabetic status, dialysis vintage and the transplanting states in the LASSO selected features.*

Figure 5

Association between various classes of the trajectories of systolic BP decline and DGF using Random Forest and Lasso selected variables (Derivation cohort)

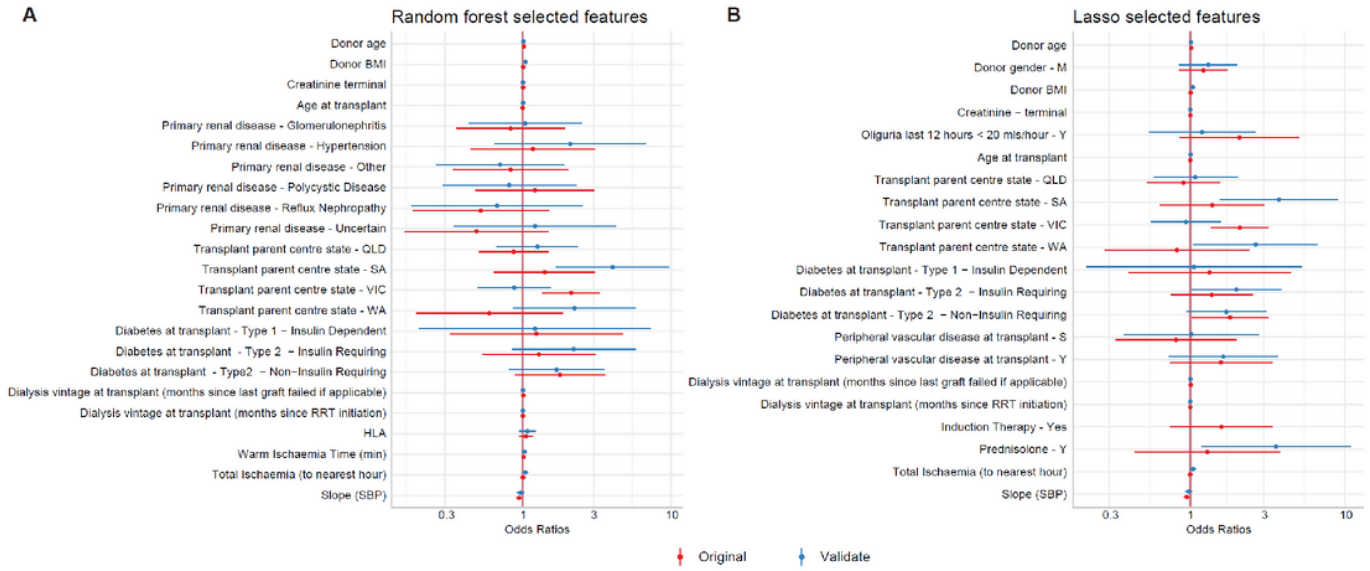


Figure 6

Association between the slope of decline of systolic blood pressure and DGF (Random Forest and Lasso selected variables in the derivation and validation cohorts)

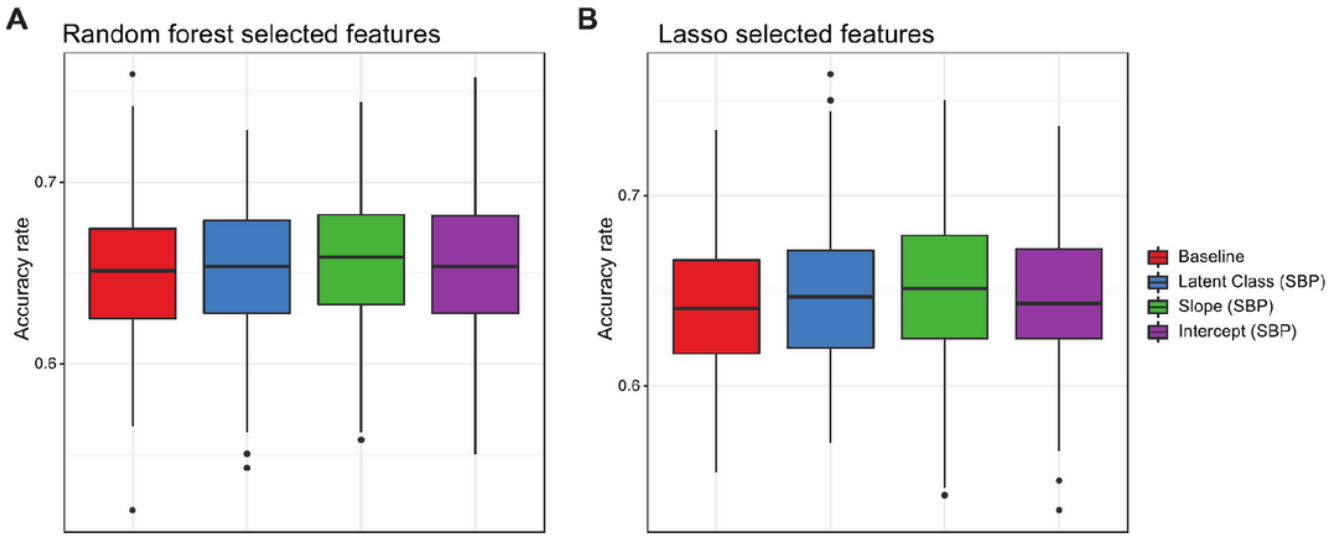


Figure 7

Performance of the derivation model using random forest and LASSO selected features

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementarytablesandfiguresDGFDCD211021.pdf