NHS BLOOD AND TRANSPLANT

CARDIOTHORACIC ADVISORY GROUP

UPDATED RISK-ADJUSTED HEART POST-TRANSPLANT SURVIVAL MODELS

SUMMARY

BACKGROUND

1. This paper presents newly developed risk adjusted heart post-transplant survival models which replace the previous models developed by the UK Cardiothoracic Transplant Audit. All models are for patient survival times.

2. These models will be used annually to estimate post-transplant survival in the Annual Report on Cardiothoracic Transplantation and will form the basis for any research project looking at the factors that influence post-transplant survival. They will also be used in the monthly CUSUM monitoring reports sent to the centres.

RESULTS

3. The table below presents the factors included in the 30-day, 1-year and 5-year heart post-transplant survival models.

Factor	Details
Donor cause of death	Vascular Trauma Hypoxic Other
Donor BMI	Continuous linear
Donor age	Continuous linear
Donor respiratory arrest	No Yes
Recipient BMI	Continuous linear
Recipient creatinine at transplant	Continuous non-linear
VAD at transplant	Short-term Long-term ECMO None
Recipient hospital status at transplant	Hospital Not in hospital
Recipient primary disease	Dilated cardiomyopathy Coronary heart disease Congenital heart disease Other
Donor (D) Recipient (R) Sex mismatch	RM : DM RM : DF RF : DM RF : DF

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Statistics and Clinical Studies **March 2016**

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BACKGROUND

1. Risk-adjusted post-transplant survival models for heart transplants are used by NHSBT in the NHS England annual organ specific report to estimate post-transplant survival at the six adult heart transplant centres. They are also used in the continuous monitoring of centre outcomes (CUSUMs) to determine whether centres' 30 day outcomes are deviating from their expected survival rates.

2. Unadjusted survival estimates are difficult to compare meaningfully due to the lack of account for centre case mix. Therefore, risk-adjusted models were developed for short-term survival following first adult heart transplant by the UK Cardiothoracic Transplant Audit (UKCTA) team based at the Royal College of Surgeons (RCS).

3. The UKCTA team developed 30 day and one year models for UK heart transplants. Until September 2015, these one year models were used to estimate one, three and five year risk-adjusted survival. The models were developed more than a decade ago (2001/2002) and required updating.

4. This paper presents newly developed models, used in the 2014/15 Annual Report on Cardiothoracic Transplantation, which replace the previous UKCTA models. All models are for patient survival times.

5. These models will be used annually to estimate post-transplant survival in the annual report and will form the basis for any research project looking at the factors that influence post-transplant survival. They will also be used in the monthly CUSUM monitoring reports sent to the centres.

COHORT

6. Data on 1,100 first adult DBD heart only transplants performed in the UK between 1 January 2004 and 31 December 2013 were obtained from the UK Transplant Registry (UKTR). Heart/lung transplants were excluded

METHODS

7. Cox proportional hazards regression models were built for 30-day, one year and five year patient survival post-transplant.

8. Clinical advice was sought as to the factors that should be considered for inclusion in a risk adjusted model for each of the time points. The factors previously found to be statistically significant were also considered and the full set of variables tested are shown in **Appendix A.** Factors which reached statistical significance at a 10% level were included in the final models.

9. For heart retrievals involving the Organ Care System (OCS), the definition of total ischaemia time used by NHSBT (cross-clamp to reperfusion) overestimates the true ischaemia time because the heart is not subject to ischaemia during transportation. As data on the usage of OCS is not currently collected by NHSBT, the inclusion of ischaemia time would be potentially more misleading than not including it if data on OCS usage could not incorporated. Thus, ischaemia time was not considered for inclusion in any of the heart models.

10. Previous analyses using cardiothoracic data from the UKTR have often been performed on a 'complete case' dataset whereby transplants are excluded if missing values exist for any of the factors included in the models. This may, however, introduce bias into the results as the missing values may not be missing completely at random. It was therefore agreed that Multiple Imputation techniques would be used to impute all missing values. The proportion of missing values for each variable is shown in **Appendix A**.

11. Multiple imputation was implemented in SAS Enterprise Guide, using chained equations. The form of the imputation model used to estimate missing values consisted of all potential variables in **Appendix A** as well as the outcome variables, survival time and censoring indicator. Twenty imputations were run with 50 burn-in iterations before each imputation. Post-transplant survival models were fitted to the resulting 20 datasets and estimates were obtained for each parameter in the model by analysing the results of these 20 models collectively.

12. During the post-transplant survival modelling process, the effect of continuous variables (say, X) on post-transplant survival was generally assumed to be linear in the model, i.e. the change in hazard of death when x is increased to $x+1$ is the same, regardless of the value of x. However, some factors were tested as non-linear variables (i.e. the change in hazard of death when x is increased to $x+1$ depends on the value of x) following clinical advice from the Clinical Audit Group. In addition, non-linearity was assessed for all continuous factors included in the final model. A natural cubic spline was used to investigate non-linearity for these factors. Splines take account of this relationship by fitting a non-linear function between each set of 'knots' at values of x which are specified by the statistician. As a general rule, four knots were used; one at each of the 5th, 35th, 65th and 95th percentile of the observed values of X.

RESULTS

13. **Table 1** presents the ten factors included in all three final heart models (30-day, 1-year, 5-year post-transplant survival). The significance of each factor for each model is indicated along with the estimated hazard ratios and corresponding 95% confidence intervals (CI's). Note that variables which were found to be significant at the 10% level for any one of the three outcomes (30-day, 1-year and 5-year) were kept in all three models.

14. While a 'VAD' factor is included in the one-year and five-year models, there were not enough events in the 'short-term' or 'long-term' VAD categories to estimate 30-day survival for these categories. The VAD factor is therefore collapsed to simply 'ECMO' versus 'No ECMO' for 30-day survival.

15. There was found to be little difference in terms of post-transplant survival between donor causes of death Vascular, Trauma or Hypoxic brain damage. Donors who experienced 'Other' causes of death were however found to be associated with a significantly different 30-day and one-year post-transplant survival. There were 81 donors in this category, 31 of which died of meningitis, 5 died of drug overdose and the remaining 45 died of causes that are not separately identified on the Core Donor Data form.

16. **Figures 1, 2** and **3** illustrate the hazard ratios and 95% CI's for the 30-day, 1-year and 5-year models respectively. A horizontal line at a value of 1 would indicate no effect.

17. **Figure 4** shows the non-linear effect of recipient creatinine upon 5-year post-transplant survival by illustrating how the hazard ratio changes dependent upon the value of recipient creatinine.

Table 1: Heart model results						
	30-day model		1-year model		5-year model	
Factor	**p-value**	**Hazard ratio (95%)**	**p-value**	**Hazard ratio (95%)**	**p-value**	**Hazard ratio (95%)**
Donor factors						
Cause of death	0.01		0.04		0.31	
Vascular		1		1		1
Trauma		0.97 (0.54,1.74)		1.22 (0.79, 1.89)		1.16 (0.81, 1.66)
Hypoxic		0.74 (0.35, 1.59)		0.91 (0.50, 1.65)		0.89 (0.55, 1.45)
Other		0.16 (0.04, 0.64)		0.47 (0.25, 0.91)		0.72 (0.46, 1.13)
Donor BMI (linear)	0.25	1.03 (0.98, 1.07)	0.03	1.04 (1.00, 1.07)	0.01	1.04 (1.01, 1.07)
Donor age (linear)	0.13	1.01 (1.00, 1.03)	0.01	1.02 (1.01, 1.03)	0.003	1.02 (1.01, 1.03)
Respiratory arrest	0.23		0.37		0.06	
No		1		1		1
Yes		1.40 (0.81, 2.43)		1.22 (0.79, 1.86)		1.39 (0.99, 1.94)
Recipient factors						
Recipient BMI (linear)	0.06	1.05 (1.00, 1.10)	0.71	1.01 (0.97, 1.05)	0.60	1.01 (0.98, 1.04)
Creatinine at transplant (non-linear)	0.91	Non-linear (non-sig)	0.74	Non-linear (non-sig)	0.03	**Figure 4**
VAD at transplant	0.02		0.06		0.26	
Short-term		No ECMO: 1 ECMO: 4.29 (1.49, 12.36)		1.5 (0.51, 4.42)		0.63 (0.26, 1.54)
Long-term				1		1
ECMO				4.63 (1.66, 12.89)		1.86 (0.76, 4.58)
None				1.55 (0.83, 2.90)		0.84 (0.56, 1.26)
Hospital status at transplant	0.08		0.47		0.68	
Hospital		0.69 (0.46, 1.05)		0.89 (0.65, 1.22)		1.06 (0.82, 1.37)
Not in hospital		1		1		1
Primary disease	0.05		0.42		0.27	
Dilated cardiomyopathy		1		1		1
Coronary heart disease		1.21 (0.71, 2.04)		1.26 (0.87, 1.84)		1.23 (0.90, 1.68)
Congenital heart disease		1.98 (0.93, 4.20)		1.34 (0.71, 2.51)		1.15 (0.65, 2.02)
Other		1.86 (1.16, 2.99)		1.30 (0.89, 1.90)		1.34 (0.98, 1.84)
Transplant factors						
Sex mismatch	0.24		0.03		0.30	
RM : DM		1		1		1
RM : DF		1.15 (0.65, 2.05)		1.08 (0.7, 1.66)		1.07 (0.75, 1.53)
RF : DM		1.89 (1.05, 3.40)		2.06 (1.33, 3.20)		1.48 (1.00, 2.19)
RF : DF		1.01 (0.58, 1.76)		1.11 (0.73, 1.69)		1.02 (0.72, 1.44)

Figure 1 30-day post heart transplant survival: risk-adjusted hazard ratios and 95% confidence limits for categorical factors

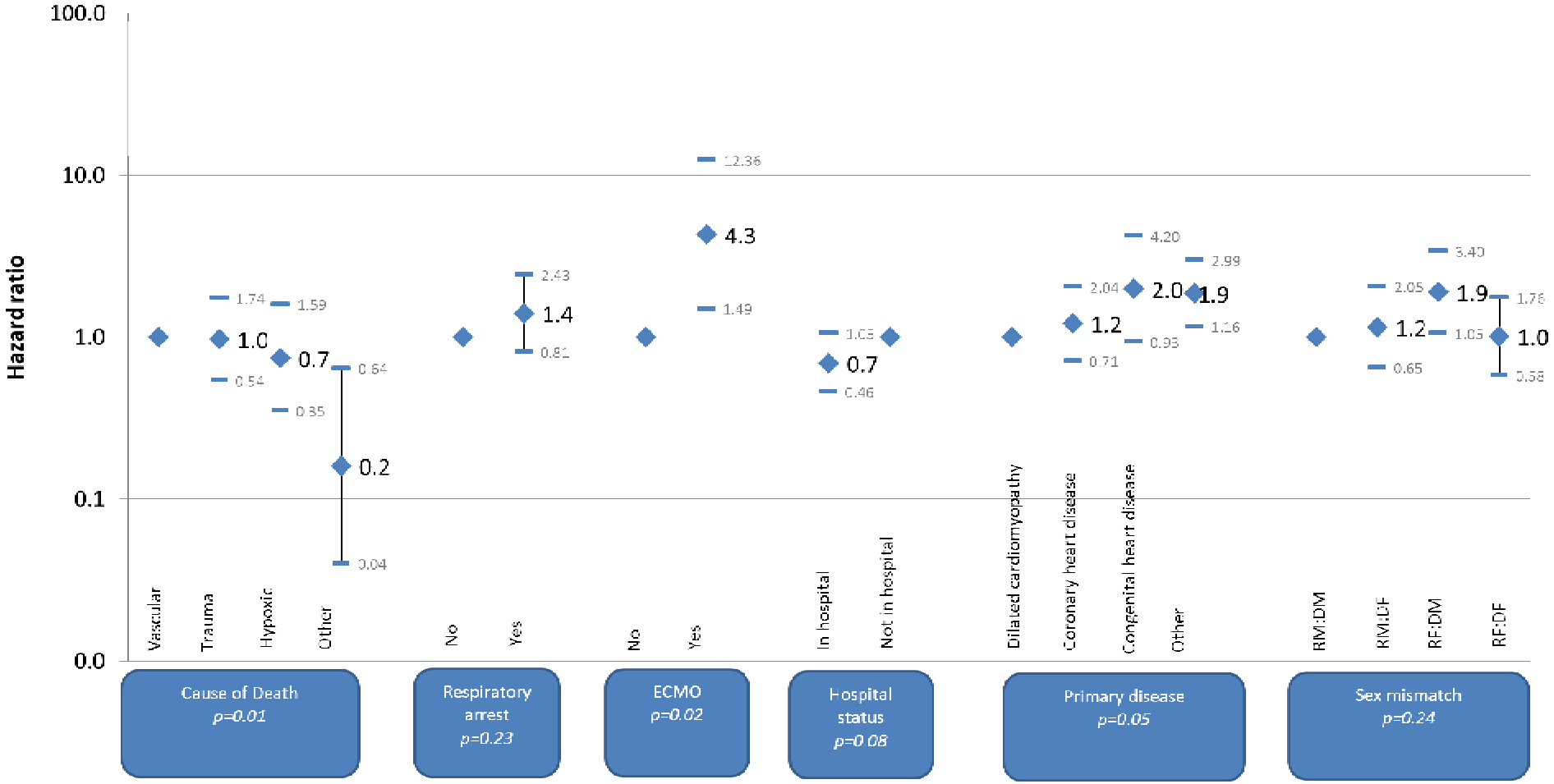


Figure 2 1- year post heart transplant survival: risk-adjusted hazard ratios and 95% confidence limits for categorical factors

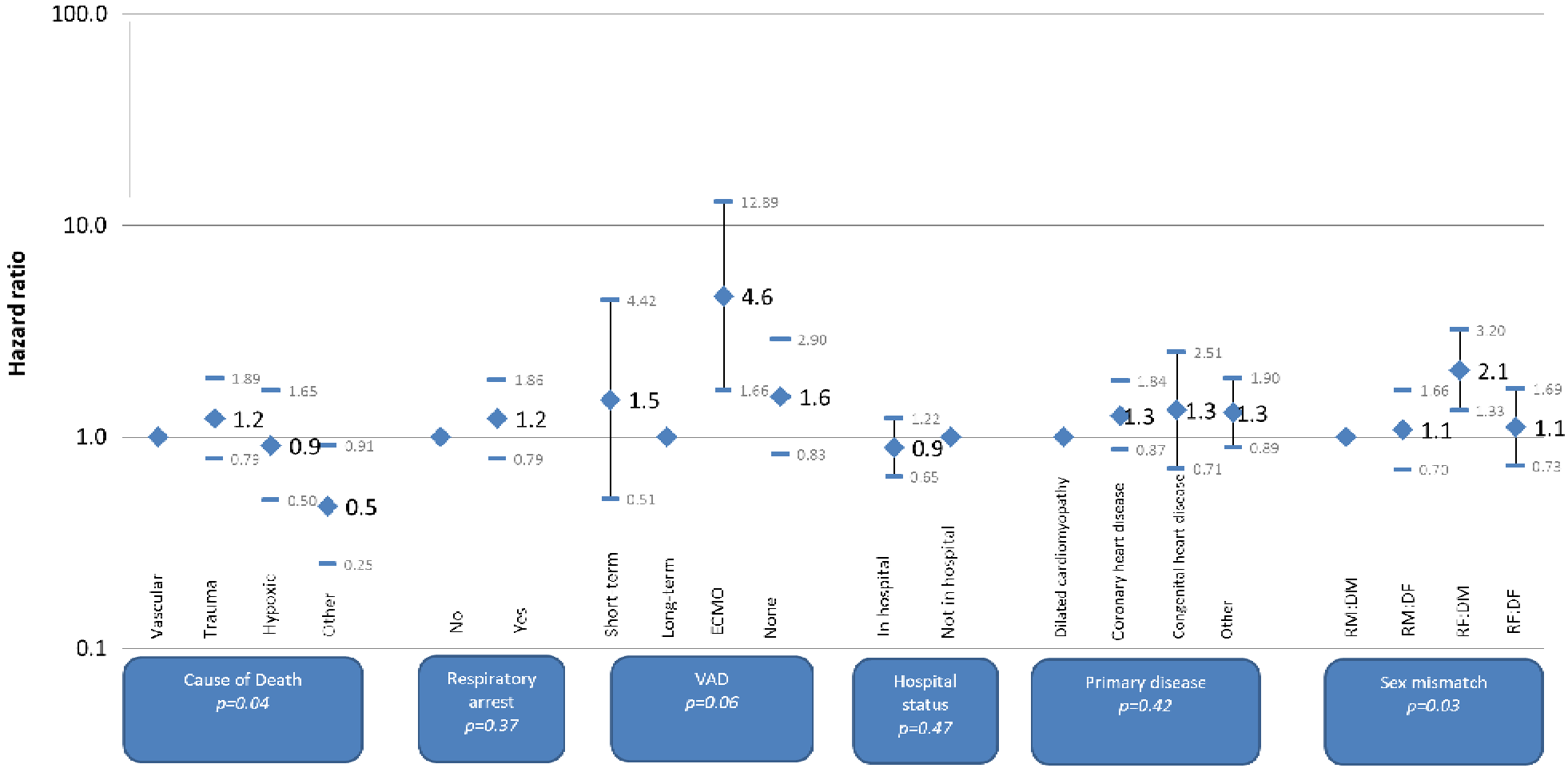


Figure 3 5-year post heart transplant survival: risk-adjusted hazard ratios and 95% confidence limits for categorical factors

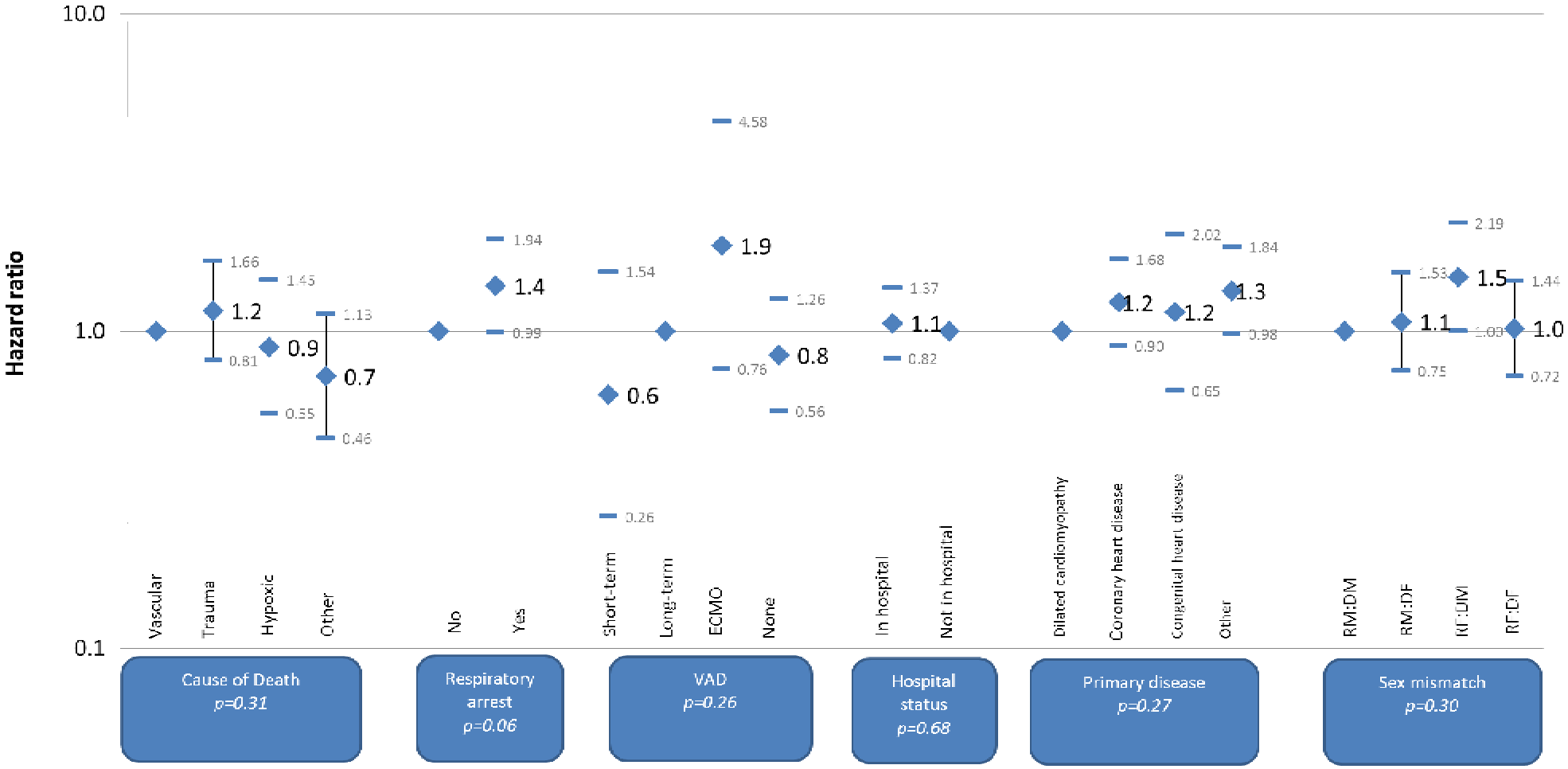
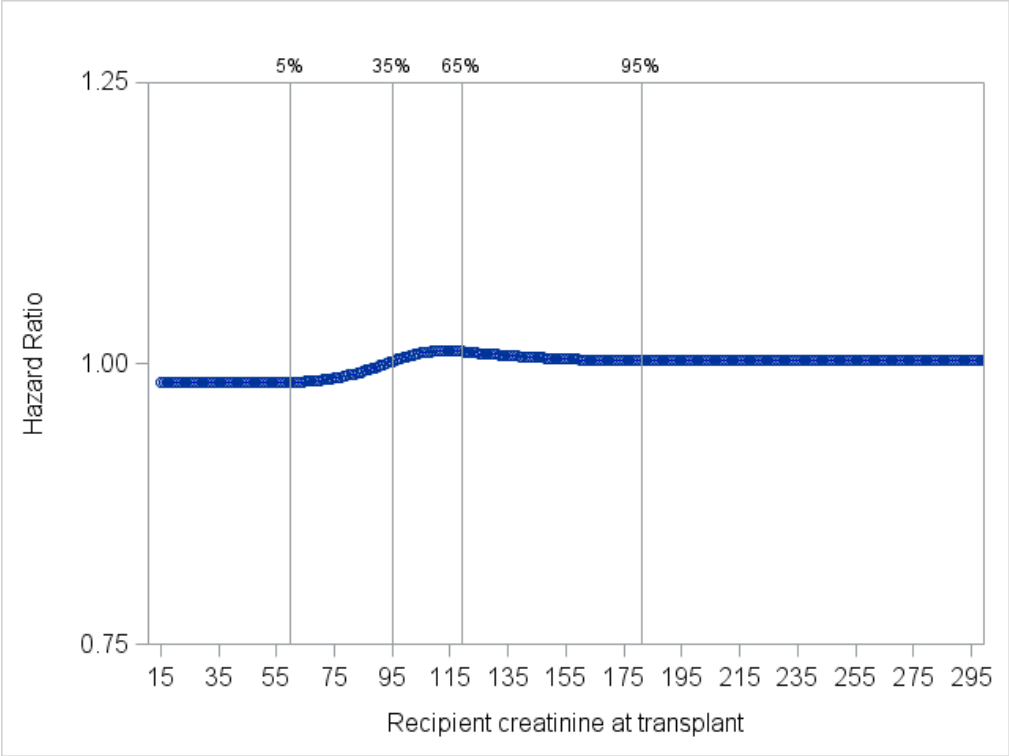


Figure 4 5-year post heart transplant survival: risk-adjusted hazard ratio for recipient creatinine at transplant



DISCUSSION

18. It is noted by the CTAG Clinical Audit Group that the heart models are grossly limited due to the exclusion of ischaemia time as a factor. NSHBT are in the process of submitting an IT proposal to collect data on OCS usage, perfusion techniques and associated ischaemia times. Once a data collection process is in place and retrospective data collected, this factor can be added to the models.

19. It is recommended that these models are reviewed and updated every three years, as a minimum, to ensure they reflect current practice.

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Appendix A) – Candidate heart factors considered

Factor	% complete N=1,100	Categorisation and % observed data in each category for categorical factors or median (IQR) and mean (SD) for continuous factors	
Donor factors			
Donor age (year)	100%	39 (28,47)	37.9 (12.2)
Donor gender	100%	Male (69%),	Female (31%)
Donor cause of death	99.6%	Vascular (62.1%) Hypoxic (8.4%) Trauma (19.7%)	Tumour (2.4%) Other (7.4%)
Donor blood group	100%	O (52%), B (9%),	A (39%), AB (0%)
Donor past history of hypertension	97%	No (90%),	Yes (10%)
Donor Cardiac arrest	95.6%	No (85%),	Yes (15%)
Donor past history of diabetes	97%	No (98%),	Yes (2%)
Donor past history of smoking	97.6%	No (52%),	Yes (48%)
Ethnic Origin	99%	White (96%),	Non-white (5%)
Donor BMI	98.7%	24.8 (22.6,27.8)	25.5 (4.3)
Respiratory arrest	94%	No (83%)	Yes (17%)
Donor history of alcohol abuse	96.6%	No (88%)	Yes (12%)
Heart rate (beats/min)	93%	94.5 (84, 105)	95(17.4)
Mean CVP (mmHg)	76.5%	8 (6,11)	8.7 (4.6)
Noradrenaline	100%	No (13%) ,	Yes (87%)
T3	100%	No (34%),	Yes (66%)
Vasopressin used	100%	No (21%),	Yes (79%)
Methyl prednisolone	100%	No (37%),	Yes (63%)
Transfusions given	95.7%	No (81%),	Yes (19%)
Surgical Factors			
Donor/Recip height mismatch (cm)	99.6%	-3 (-10,3)	-3.6 (9.2)
Donor/recip weight mismatch *kg)	99.6%	-3 (-14, 7)	-4 (15.9)
Sex mismatch	100%	R M : D M (59%) R M : D F (14%)	R F : D F (17%) R F : D M (10%)
Blood group identical vs compatible	100%	Compatible (20%)	Identical (80%)

Factor	**% complete** **N=1,100**	**Categorisation and % observed data in each category for categorical factors or median (IQR) and mean (SD) for continuous factors**	
Recipient factors			
Height (cm)	100%	172 (165, 178)	171.4 (9.3)
Weight (kg)	99.6%	74 (64,83)	74 (14.2)
BMI	99.6%	25 (22.1, 28)	25.1 (4.03)
Age (years)	100%	48 (37, 56)	45.4 (13.4)
Sex	100%	Male (73.5%),	Female (26.5%)
Primary Disease	99.9%	Coronary heart disease (19.6%) Valvular heart disease (1.7%) Congenital heart disease (5.8%) Dilated cardiomyopathy (56.6%) Hypertrophic cardiomyopathy (5.8%) Restrictive cardiomyopathy (2.6%) Other (7.9%)	
No. previous open heart surgeries	99%	No previous heart surgery (74%) At least 1 previous heart surgery (26%)	
Diabetes	99.4%	No (91%), Yes- insulin dependent (3%), Yes- not insulin dependent (6%)	
AICD at registration	99.3%	No (65%)	Yes (35%)
Creatinine (µmol/l)	98.7%	106 (86, 130)	113.7 (48.2)
Creatinine clearance	98.5%	75 (57.6, 99.6)	81.7 (36.6)
eGFR	98.7%	64.8 (50.6, 84.1)	71.4 (36.4)
Antiarrhythmics (excluding digoxin)	98.5%	No (64%)	Yes (36%)
On inotropes at transplant?	99.6%	No (66%)	Yes (34%)
On IABP at transplant?	99.6%	No (89%)	Yes (11%)
VAD	100%	Long-term VAD (9%) Short-term VAD (3.4%) ECMO (1.4%) No VAD (86.2%)	
ECMO at transplant	100%	Yes (1.4%)	No (98.6%)
Ventilated at transplant?	99.6%	No (98%)	Yes (2%)
In hospital pre transplant?	99.6%	No (46%)	Yes (54%)
Infection requiring IV antibiotics in last 6 weeks	99.3%	No (80%)	Yes (20%)
Urgent status of transplant	100%	Non-urgent (53%)	Urgent (47%)

Factor	**% complete** **N=1,100**	**Categorisation and % observed data in each category for categorical factors or median (IQR) and mean (SD) for continuous factors**	
PA systolic at registration (mmHg)	88.4%	43 (33,52)	42.8 (13.5)
PA mean at registration (mmHg)	82%	30 (23, 37)	30.2 (11.02)
PCW or LAP at registration (mmHg)	88%	23 (17,29)	22.98 (8.9)
Cardiac output at registration (l/min)	78.7%	3.2 (2.5, 4)	3.4 (1.2)