

NHS BLOOD AND TRANSPLANT

CARDIOTHORACIC ADVISORY GROUP – HEART

Heart waiting list modelling for Transplant Risk Communication Tool

Non-urgent heart registrations – modelling summary

Cohort

Patients aged ≥ 16 years at one of the 6 UK adult centres, registered between 1 January 2012 and 31 December 2018. NHS Group 2 patients, multi-organ registrations, patients who had a previous transplant, and registrations ending in a DCD heart transplant were excluded. Time from first non-urgent registration to waiting list outcome within 3 years was modelled (any patient not reaching an outcome by 3 years was censored at 3 years).

Possible patient outcomes, within three years after first non-urgent heart registration

- Transplanted
- Died OR removed from list
- Moved to a higher-urgency list (urgent or super-urgent)
- Remained on non-urgent list

Three Cox models were fitted: 1) time to transplant, with all other outcomes treated as censored; 2) time to death / removal, with all other outcomes treated as censored; 3) time to moving to higher urgency list, with all other outcomes treated as censored.

All models were stratified by transplant centre (i.e. each centre has its own baseline hazard function, but covariate effects are assumed to be the same across all centres).

Candidate variables

Candidate variable	Possible values	Treatment of missing data
Previous registration	yes; no	N/A – no missing values
Era of registration	2012-2014; 2015-2016; 2017-2018	N/A – no missing values
Sex	female; male	set to “male”
Age group	16-29; 30-39; 40-49; 50-59; 60+	N/A – no missing values
Ethnicity	white; Asian, black, mixed or other	set to “white”
Blood group	A or AB; B; O	N/A – no missing values
Primary disease	coronary heart disease; cardiomyopathy; congenital heart disease; other/regraft	set to “cardiomyopathy”
CMV positivity	yes; no; missing or unknown	keep separate “missing or unknown” category
Height	<170cm; 170-179cm; 180cm and above	set to “170-179cm”

Weight	<65kg; 65 to <76 kg; 76 to <87 kg; 87kg and above	set to correspond to BMI 25 to <30
BMI	<25; 25 to <30; 30 and above	set to "25 to <30"
eGFR	90ml/min or above; 60 to 89 mL/min; 45 to 59 mL/min; 44 mL/min or below	set to "60 to 89 mL/min"
Bilirubin	<1 mg/dL; 1 to <2 mg/dL; 2 mg/dL and above	set to "<1 mg/dL"
On MCS (long-term VAD)	yes; no	set to "no"
In hospital status	yes; no	set to "no"
Cerebrovascular disease	yes; no	set to "no"
Cholesterol	normal (up to 5.0 mmol/L); high (>5.0 mmol/L); missing or unknown	included in "missing or unknown" category
Diabetes	yes; no	set to "no"

NB: peripheral vascular disease and other positive virology (non-CMV, i.e. HIV, HCV or HBV) were only present in 8 and 15 patients respectively, so not included in the list of candidate variables.

Summary of patient outcomes at 3 years, by transplant centre

Centre	Transplanted	Died	Removed*	Moved to a higher-urgency list**	Still on non-urgent list	Total
Birmingham	19	11	32	49	32	143
Glasgow	17	0	20	17	12	66
Harefield	15	15	23	55	44	152
Manchester	24	6	11	43	30	114
Newcastle	22	54	10	65	46	197
Papworth	60	19	16	71	8	174
TOTAL	157	105	112	300	172	846

* includes due to condition deteriorated, condition improved, or unknown reason

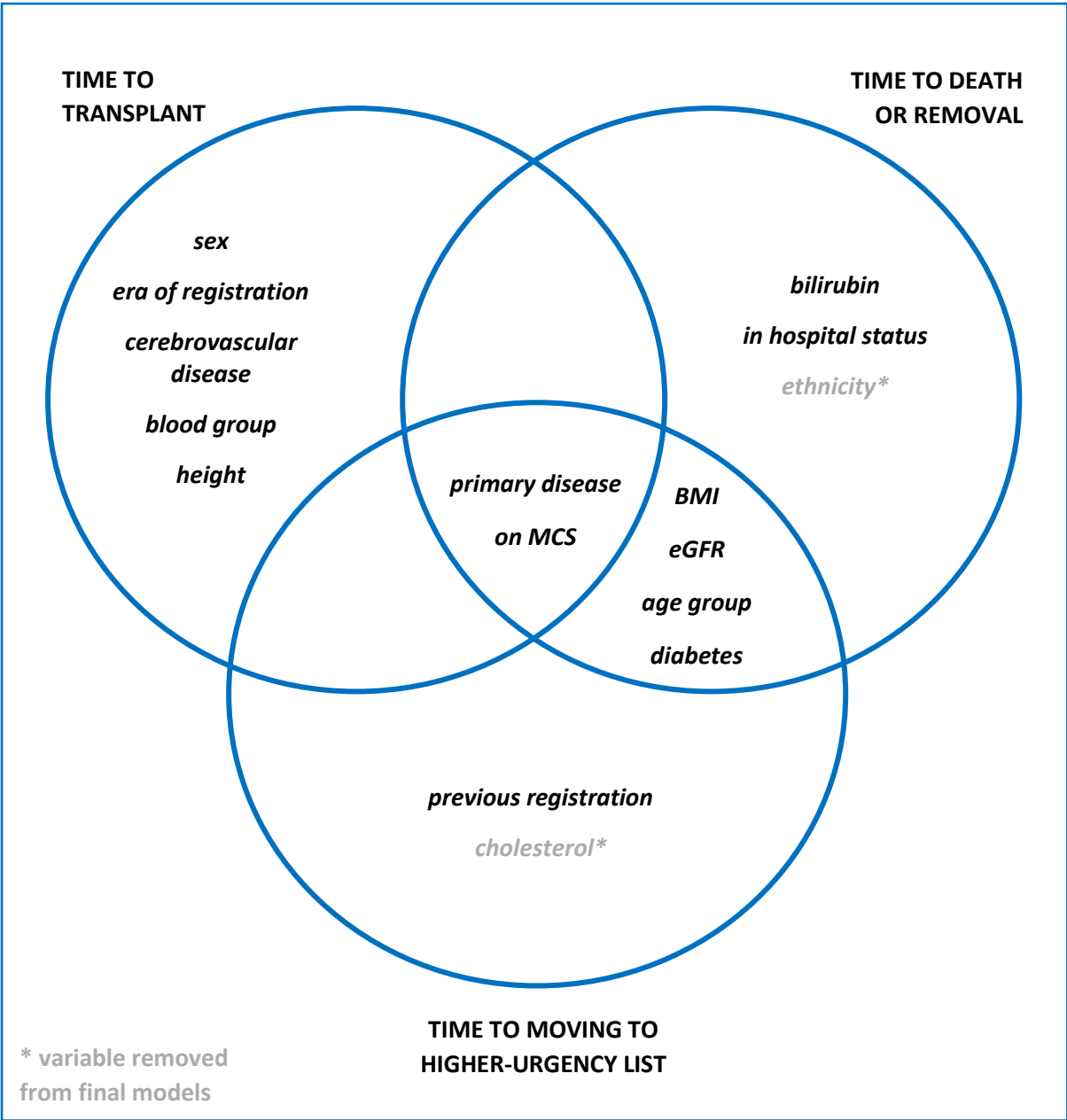
** i.e. moved to the urgent or super-urgent list

Selected variables

The final clean dataset of first non-urgent registrations contained 846 records. This was split (70:30) into a model-building cohort (n = 601) and a validation cohort (n = 245). Models for the three outcomes (time to transplant, time to death or removal, time to moving to higher-urgency list) were selected independently (using a threshold p-value of 0.15 for entry/retention), and so contained different sets of covariates.

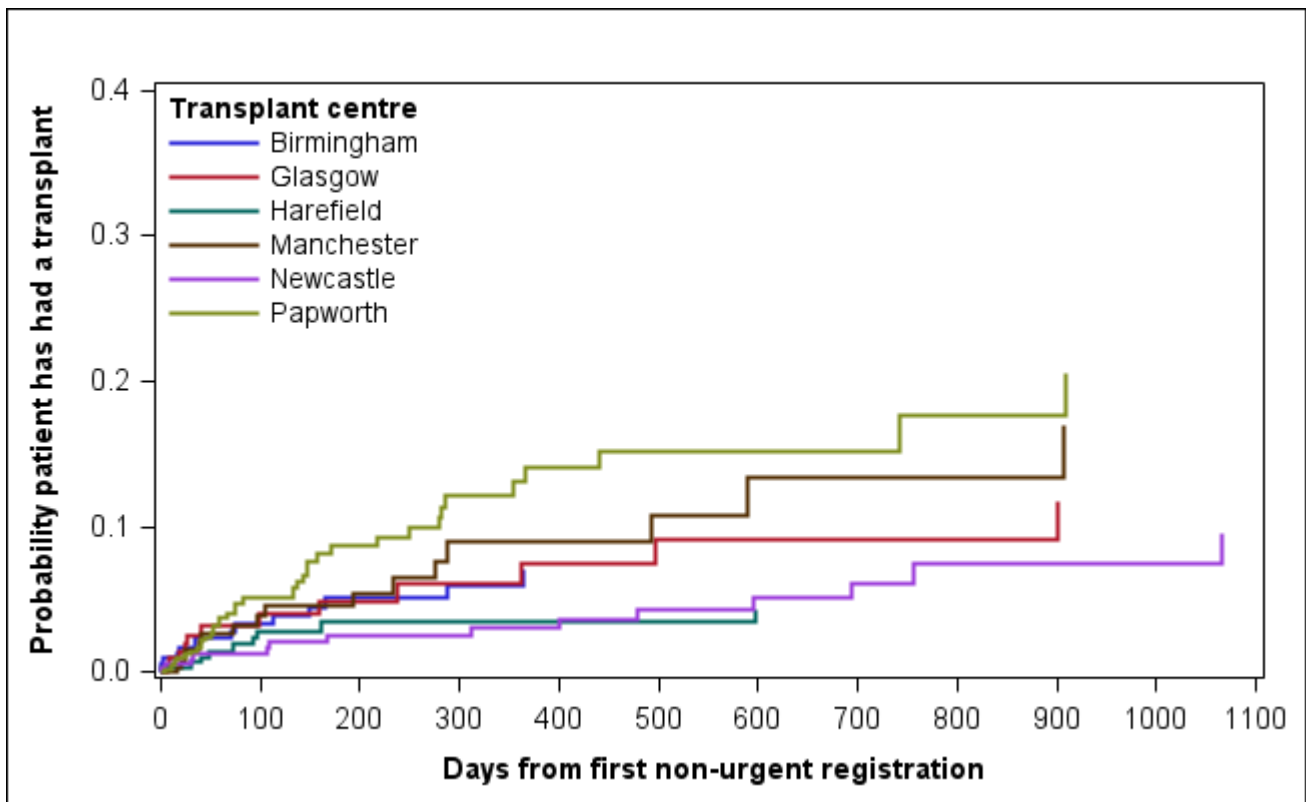
The final models for each outcome were constructed by including all variables present in any of the three models selected independently. At this stage, to reduce model complexity and risk of over-fitting, any variable not reaching a significance threshold of $p < 0.1$ in at least one model was removed: this "pruning" step excluded ethnicity and cholesterol.

The Venn diagram on the next page illustrates which variables were predictive of which outcome(s).

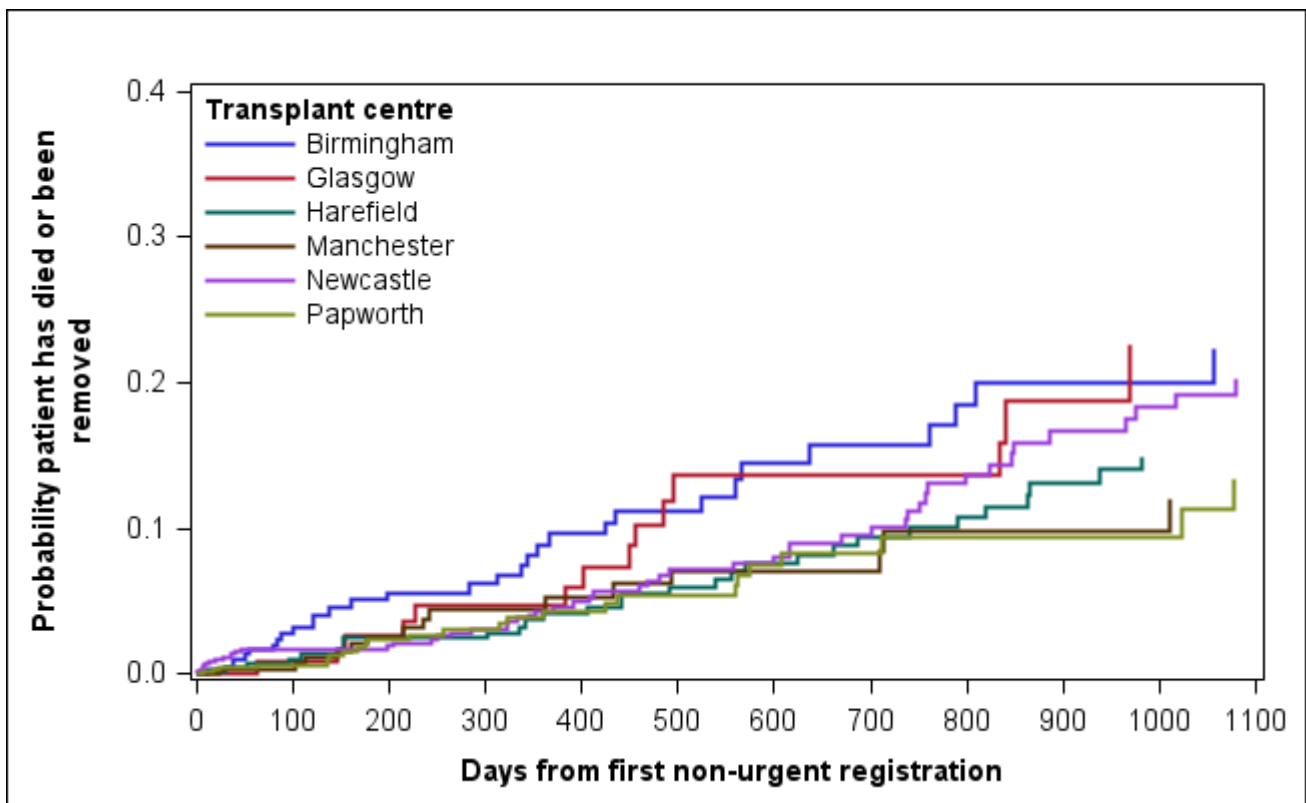


Candidate variables not selected in any model: CMV positivity, weight.

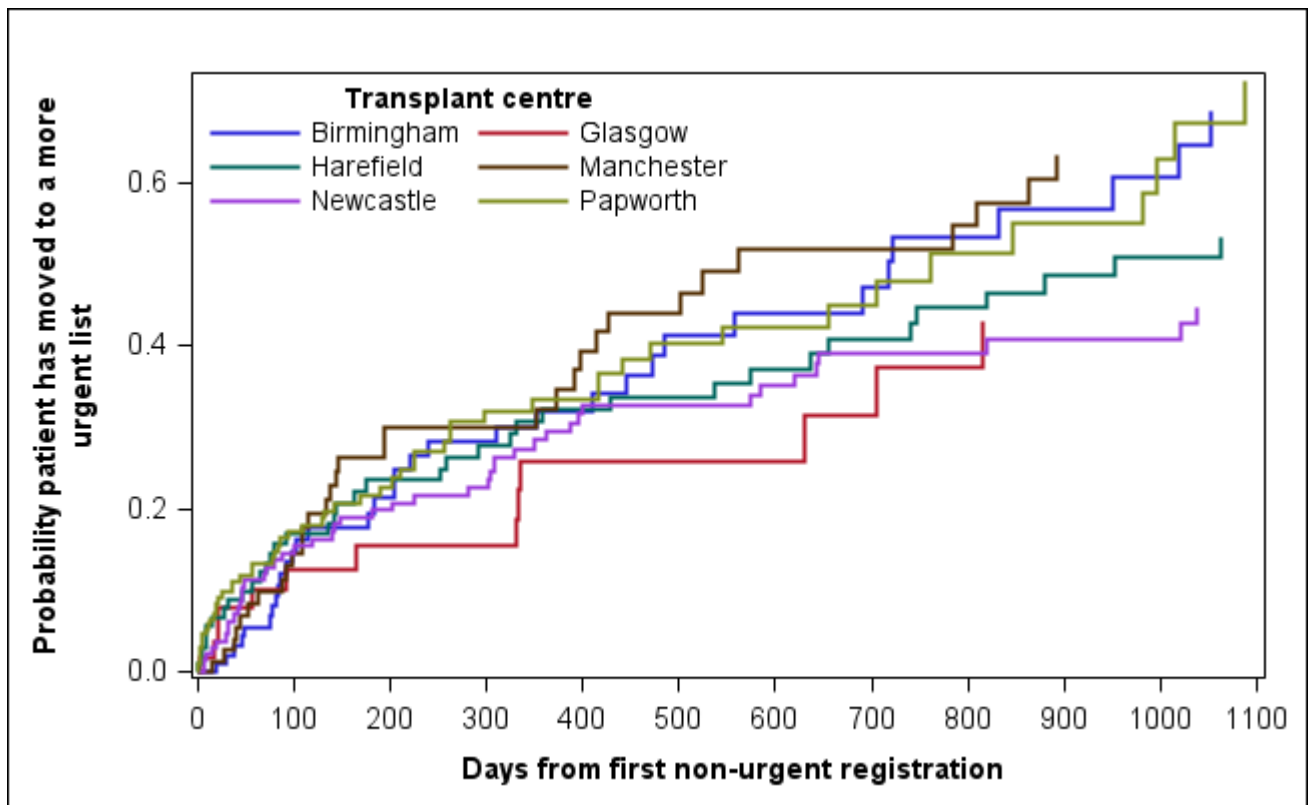
Baseline survival curves: time to transplant



Baseline survival curves: time to death or removal



Baseline survival curves: time to moving to a higher-urgency list



Hazard ratios from all three final models

Variable	Category	Time to transplant model		Time to death or removal model		Time to higher urgency model	
		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Sex (baseline = male)	female	1.99 (1.15, 3.45)	0.0142	1.45 (0.84, 2.48)	0.1807	0.86 (0.53, 1.39)	0.5314
Age group (baseline = 50-59)	16-29 30-39 40-49 60+	0.47 (0.18, 1.21) 1.24 (0.65, 2.37) 0.96 (0.54, 1.69) 0.92 (0.50, 1.67)	0.4031	1.12 (0.54, 2.31) 0.78 (0.40, 1.52) 1.17 (0.75, 1.82) 1.78 (1.17, 2.70)	0.0444	1.54 (0.93, 2.53) 0.88 (0.55, 1.40) 0.79 (0.53, 1.16) 0.59 (0.38, 0.91)	0.0128
Previous registration (baseline = no)	yes	0.65 (0.14, 3.01)	0.5847	0.87 (0.42, 1.80)	0.7048	1.85 (1.03, 3.30)	0.0385
Era of registration (baseline = 2017-2018)	2012-2014 2015-2016	2.50 (1.41, 4.44) 1.69 (0.86, 3.29)	0.0058	1.35 (0.90, 2.03) 1.26 (0.80, 1.98)	0.3324	1.13 (0.80, 1.58) 0.92 (0.62, 1.36)	0.5184
Blood group (baseline = O)	A or AB B	3.54 (2.14, 5.83) 3.21 (1.54, 6.68)	< 0.0001	1.18 (0.84, 1.66) 0.81 (0.44, 1.50)	0.3928	0.85 (0.63, 1.14) 1.16 (0.73, 1.83)	0.3335
Primary disease (baseline = cardiomyopathy)	congenital HD coronary HD other / regrant	0.34 (0.12, 0.99) 0.80 (0.47, 1.35) 0.41 (0.12, 1.43)	0.1168	0.40 (0.18, 0.90) 0.75 (0.50, 1.12) 0.78 (0.37, 1.63)	0.0963	0.70 (0.41, 1.19) 0.59 (0.39, 0.88) 0.74 (0.40, 1.38)	0.0416
Height (baseline = 170-179cm)	<170cm 180cm and above	1.62 (0.93, 2.83) 0.46 (0.23, 0.91)	0.0049	0.89 (0.54, 1.46) 1.20 (0.82, 1.76)	0.4914	1.00 (0.64, 1.56) 1.02 (0.73, 1.43)	0.9912
BMI (baseline = 25 to < 30)	< 25 30 or higher	1.13 (0.70, 1.85) 0.92 (0.54, 1.57)	0.7709	2.17 (1.46, 3.22) 1.54 (1.02, 2.33)	0.0006	1.55 (1.13, 2.14) 0.90 (0.60, 1.33)	0.0075
eGFR (baseline = ≥ 90mL/min)	60 to 89 mL/min 45 to 59 mL/min ≤ 44 mL/min	0.70 (0.37, 1.31) 0.75 (0.36, 1.53) 0.75 (0.31, 1.80)	0.7420	1.44 (0.82, 2.54) 2.03 (1.08, 3.84) 3.01 (1.54, 5.87)	0.0040	1.27 (0.82, 1.97) 1.87 (1.12, 3.11) 1.97 (1.09, 3.55)	0.0353
Bilirubin (baseline = < 1 mg/dL)	1 to < 2 mg/dL 2 mg/dL and above	0.82 (0.49, 1.38) 1.55 (0.76, 3.18)	0.2657	1.36 (0.94, 1.97) 1.93 (1.14, 3.27)	0.0337	1.11 (0.81, 1.51) 0.69 (0.39, 1.21)	0.2702
On MCS (baseline = no)	yes	0.40 (0.20, 0.80)	0.0090	0.42 (0.27, 0.64)	< 0.0001	0.37 (0.25, 0.56)	< 0.0001
In hospital status (baseline = no)	yes	0.59 (0.24, 1.43)	0.2428	2.92 (1.91, 4.46)	< 0.0001	1.45 (0.97, 2.16)	0.0688
Cerebrovascular disease (baseline = no)	yes	2.21 (1.07, 4.58)	0.0329	0.76 (0.34, 1.69)	0.5021	0.97 (0.53, 1.78)	0.9323
Diabetes (baseline = no)	yes	1.01 (0.52, 1.96)	0.9839	1.40 (0.90, 2.17)	0.1372	0.59 (0.35, 0.98)	0.0405

Model validation

To assess the predictive accuracy of these models, Harrell's c-statistic was calculated for both the original model-building dataset (in-sample) and the separate validation dataset (out-of-sample).

Model for time to transplant:

- in-sample c-statistic = 0.77
- out-of-sample c-statistic = 0.76

Model for time to death or removal:

- in-sample c-statistic = 0.73
- out-of-sample c-statistic = 0.62

Model for time to moving to a higher-urgency list:

- in-sample c-statistic = 0.67
- out-of-sample c-statistic = 0.66

Urgent heart registrations – modelling summary

Cohort

Patients aged ≥ 16 years at one of the 6 UK adult centres, registered between 1 January 2012 and 31 December 2018. NHS Group 2 patients, multi-organ registrations, patients who had a previous transplant, and registrations ending in a DCD heart transplant were excluded. Time from first urgent registration to waiting list outcome within 1 year was modelled (any patient not reaching an outcome by 1 year was censored at 1 year).

Possible patient outcomes, within one year after first urgent heart registration

- Transplanted
- Died OR removed from list with condition deteriorated/unknown OR moved to the super-urgent list
- Remained on urgent list OR removed from list with condition improved OR moved to the non-urgent list

Two Cox models were fitted: 1) time to transplant, with all other outcomes treated as censored; 2) time to death or deterioration, with all other outcomes treated as censored.

Both models were stratified by transplant centre (i.e. each centre had its own baseline hazard function, but covariate effects were assumed to be the same across all centres).

Candidate variables

Candidate variable	Possible values	Treatment of missing data
Previous registration	yes; no	N/A – no missing values
Era of registration	2012-2014; 2015-2016; 2017-2018	N/A – no missing values
Sex	female; male	N/A – no missing values
Age group	16-29; 30-39; 40-49; 50-59; 60+	N/A – no missing values
Ethnicity	white; Asian, black, mixed or other	set to “white”
Blood group	A; AB; B; O	N/A – no missing values
Primary disease	coronary heart disease; cardiomyopathy; congenital heart disease; other/regraft	N/A – no missing values
CMV positivity	yes; no; missing or unknown	keep separate “missing or unknown” category
Height	<170cm; 170-179cm; 180cm and above	N/A – no missing values
Weight	<65kg; 65 to <76 kg; 76 to <87 kg; 87kg and above	set to correspond to normal BMI for height
BMI	<20; 20 to <25; 25 to <30; 30 and above	set to “20 to <25”
eGFR	90ml/min or above; 60 to 89 ml/min; 45 to 59 ml/min; 44 ml/min or below	set to “60 to 89 ml/min”
Bilirubin	<1 mg/dL; 1 to <2 mg/dL; 2 mg/dL and above	set to “<1 mg/dL”
Reason for urgent listing	adult on IV inotropes or IABP; adult on long-term VAD or TAH with complications; other or missing	included in “other or missing” category
In hospital status	yes; no	set to “yes”

Cerebrovascular disease	yes; no	set to “no”
Cholesterol	normal (up to 5.0 mmol/L); high (>5.0 mmol/L); missing or unknown	keep separate “missing or unknown” category
Diabetes	yes; no	set to “no”

NB: peripheral vascular disease and other positive virology (non-CMV, i.e. HIV, HCV or HBV) were only present in 9 and 12 patients respectively, so not included in the list of candidate variables.

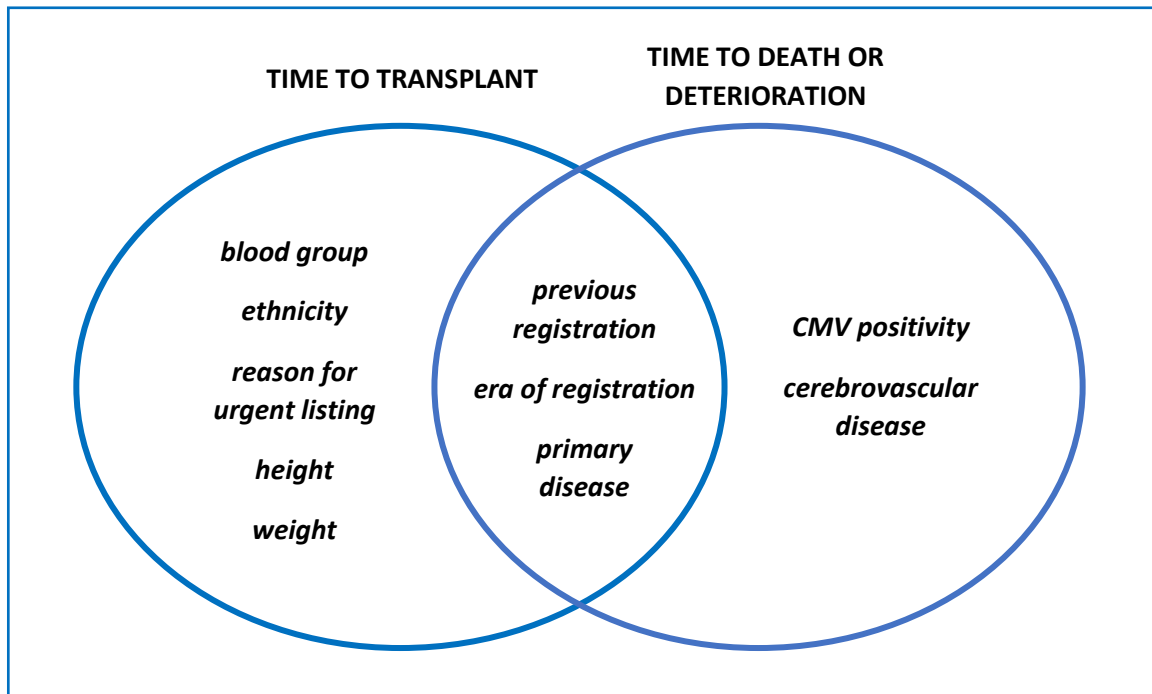
The set of candidate variables is very similar to that used for the non-urgent models, with the reason for urgent registration replacing whether or not the patient was on mechanical circulatory support at registration. In a few cases the categories are slightly different, reflecting the different characteristics of the urgent cohort of patients.

Summary of patient outcomes at 1 year, by transplant centre

Centre	Transplanted	Died or deteriorated			Still on urgent list or improved			Total
		Died	Removed, deteriorated or unknown	Moved to super-urgent list	Removed, improved	Moved to non-urgent list	Still on urgent list	
Birmingham	115	7	20	4	0	5	0	151
Glasgow	41	2	17	5	1	1	0	67
Harefield	115	8	16	5	1	8	5	158
Manchester	108	3	16	3	0	0	0	130
Newcastle	107	15	25	3	1	11	2	164
Papworth	117	6	17	3	1	10	0	154
TOTAL	603	41	111	23	4	35	7	824

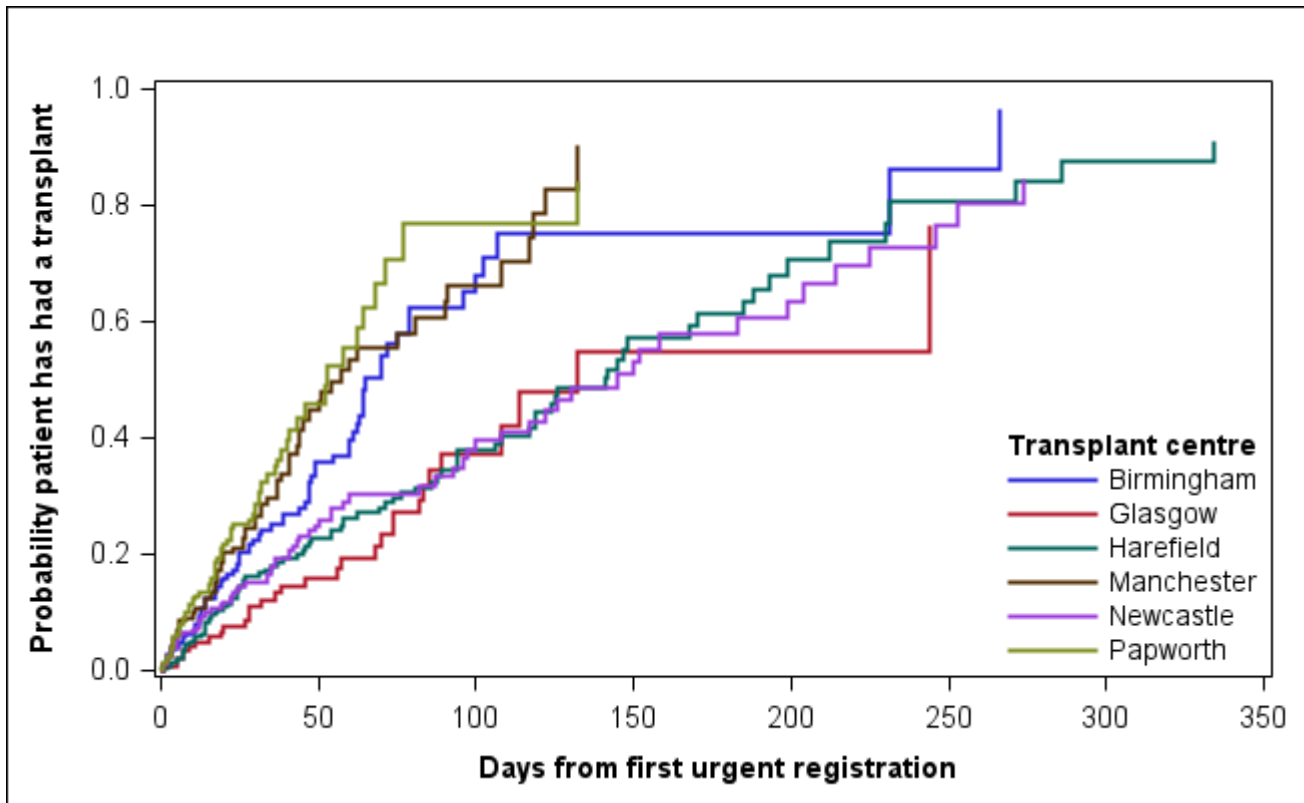
Selected variables

The final clean dataset of first urgent registrations contained 824 records. This was split (70:30) into a model-building cohort (n = 586) and a validation cohort (n = 238). Models for the two outcomes (time to transplant, time to death or deterioration) were selected independently (using a threshold p-value of 0.15 for entry/retention), and so contained different sets of covariates. The final models both contained all variables present in either of the independently-selected models.

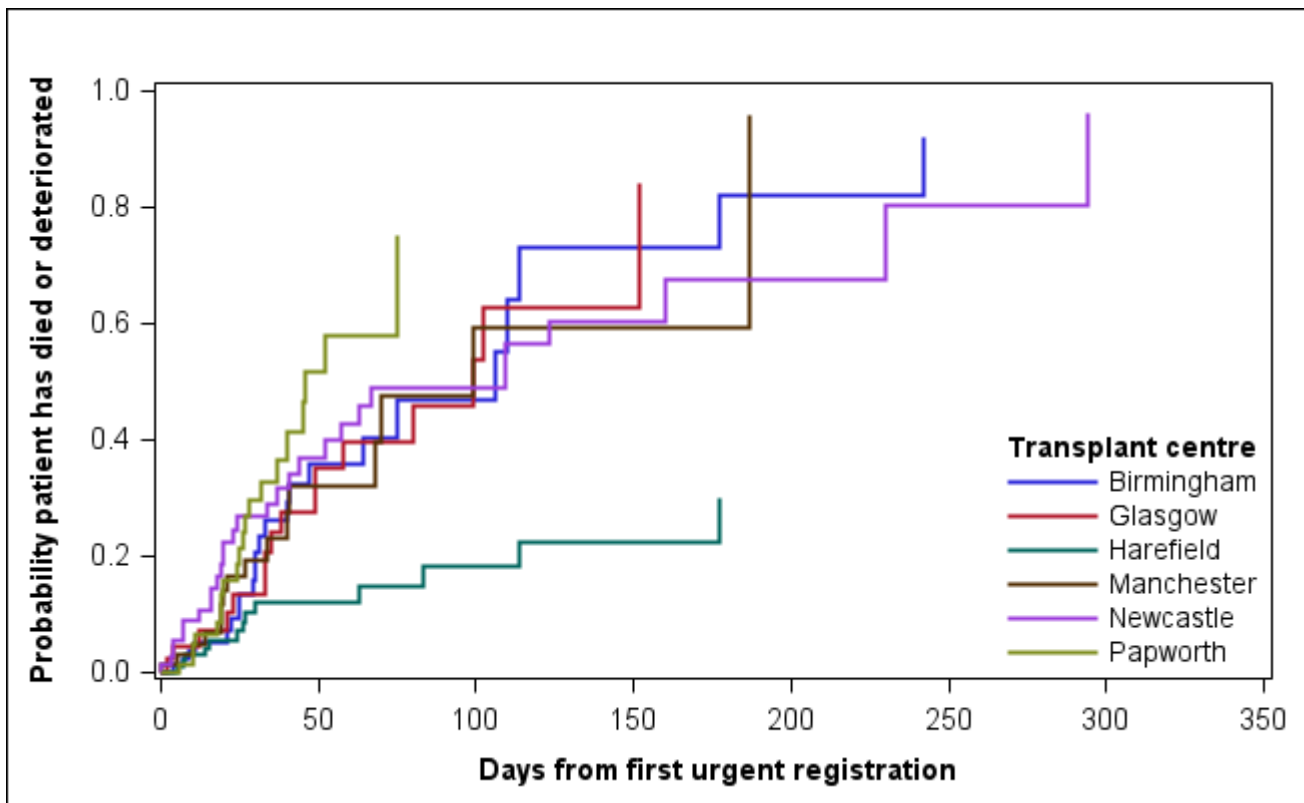


Candidate variables not selected in either model: sex, age group, BMI, eGFR, bilirubin, in hospital status, cholesterol, diabetes.

Baseline survival curves: time to transplant



Baseline survival curves: time to death or deterioration



Hazard ratios from both final models

Variable	Category	Time to transplant model		Time to death or deterioration model	
		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Previous registration (baseline = no)	yes	1.14 (0.91, 1.42)	0.2488	0.47 (0.29, 0.75)	0.0015
Era of registration (baseline = 2017-2018)	2012-2014	1.94 (1.50, 2.52)	< 0.0001	1.14 (0.72, 1.82)	0.0214
	2015-2016	1.77 (1.36, 2.31)		0.55 (0.31, 0.95)	
Ethnicity (baseline = white)	Asian, black, mixed or other	0.79 (0.58, 1.08)	0.1346	1.28 (0.70, 2.34)	0.4196
Blood group (baseline = O)	A	2.43 (1.93, 3.05)	< 0.0001	1.33 (0.86, 2.05)	0.2650
	AB	2.33 (1.43, 3.81)		1.44 (0.54, 3.83)	
	B	1.50 (1.07, 2.11)		0.72 (0.38, 1.37)	
Primary disease (baseline = cardiomyopathy)	coronary HD	0.74 (0.55, 1.00)	0.0285	1.02 (0.59, 1.75)	0.0532
	congenital HD	0.65 (0.45, 0.93)		0.33 (0.14, 0.80)	
	other/regraft	1.12 (0.73, 1.73)		0.46 (0.14, 1.50)	
CMV positivity (baseline = no)	yes	1.09 (0.87, 1.35)	0.7440	0.60 (0.39, 0.94)	0.0290
	missing/unknown	1.07 (0.69, 1.65)		0.39 (0.14, 1.10)	
Height (baseline = 170-179cm)	<170cm	1.11 (0.87, 1.43)	0.0182	1.12 (0.66, 1.91)	0.8976
	180cm and above	0.72 (0.56, 0.94)		1.08 (0.67, 1.75)	
Weight (baseline = 65 to <76kg)	<65kg	1.68 (1.24, 2.27)	0.0002	1.17 (0.61, 2.24)	0.9038
	76 to <87 kg	1.05 (0.79, 1.39)		1.22 (0.70, 2.14)	
	87kg and above	0.78 (0.58, 1.06)		1.08 (0.61, 1.91)	
Reason for urgent listing (baseline = inotropes / IABP)	VAD / TAH	0.55 (0.38, 0.79)	0.0045	1.33 (0.71, 2.49)	0.4227
	other or missing	0.94 (0.66, 1.32)		0.77 (0.36, 1.66)	
Cerebrovascular disease (baseline = no)	yes	1.33 (0.87, 2.04)	0.1934	3.27 (1.56, 6.87)	0.0018

Model validation

To assess the predictive accuracy of these models, Harrell's c-statistic was calculated for both the original model-building dataset (in-sample) and the separate validation dataset (out-of-sample).

Model for time to transplant:

- in-sample c-statistic = 0.69
- out-of-sample c-statistic = 0.65

Model for time to death or deterioration:

- in-sample c-statistic = 0.67
- out-of-sample c-statistic = 0.51