Risk Adjustment for Survival after Heart Transplantation

Unadjusted and risk-adjusted survival after first adult DBD heart transplant is presented in the annual NHS BT report on cardiothoracic organ transplantation. Risk-adjusted survival is an estimate of the survival rate at a centre if they had the same mix of patients as seen nationally.

Four centres (Papworth, Newcastle, Manchester, Birmingham) have less than 1.5% difference between unadjusted and risk-adjusted survival at 30 days, 90 days and 1 year. Glasgow's unadjusted survival is 5-6% higher than risk-adjusted survival at each time point. Harefield's unadjusted survival is 6-10% lower than their risk-adjusted survival at each time point.

Table 6.1 30 day patient survival rates after first adult DBD heart transplant, by centre, 1 April 2014 to 31 March 2018

Centre	Number of transplants	% 30 day survival (95% CI) Unadjusted		Risk-adjusted	
Birmingham	102	89.2	(81.4 - 93.9)	88.7	(79.6 - 93.7)
Glasgow	45	86.7	(72.7 - 93.8)	78.5	(52.2 - 90.3)
Harefield	96	83.3	(74.2 - 89.4)	88.4	(81.1 - 92.9)
Manchester	97	94.8	(88.1 - 97.8)	93.9	(85.4 - 97.5)
Newcastle	85	89.4	(80.6 - 94.3)	89.1	(79.1 - 94.3)
Papworth	141	94.3	(89.0 - 97.1)	94.2	(88.4 - 97.1)
UK	**566**	**90.3**	**(87.5 - 92.5)**		

Centre has reached the lower 99.8% confidence limit
Centre has reached the lower 95% confidence limit
Centre has reached the upper 95% confidence limit
Centre has reached the upper 99.8% confidence limit

Table 6.2 90 day patient survival after first adult DBD heart transplant, by centre, 1 April 2014 and 31 March 2018

Centre	Number of transplants	% 90 day survival (95% CI) Unadjusted		Risk-adjusted	
Birmingham	102	85.3	(76.8 - 90.9)	84.3	(74.0 - 90.6)
Glasgow	45	84.4	(70.1 - 92.3)	78.4	(54.7 - 89.7)
Harefield	96	76.0	(66.2 - 83.4)	84.3	(76.4 - 89.6)
Manchester	97	91.8	(84.2 - 95.8)	90.6	(81.1 - 95.3)
Newcastle	85	85.9	(76.5 - 91.7)	85.1	(73.7 - 91.5)
Papworth	141	92.2	(86.4 - 95.6)	91.3	(84.2 - 95.2)
UK	**566**	**86.6**	**(83.5 - 89.1)**		

Centre has reached the lower 99.8% confidence limit
Centre has reached the lower 95% confidence limit
Centre has reached the upper 95% confidence limit
Centre has reached the upper 99.8% confidence limit

Table 6.3 1 year patient survival rates after first adult DBD heart transplant, by centre, 1 April 2014 to 31 March 2018

Centre	Number of transplants	% 1 year survival (95% CI) Unadjusted		Risk-adjusted	
Birmingham	102	81.3	(72.3 - 87.6)	79.9	(68.5 - 87.2)
Glasgow	45	81.8	(66.8 - 90.5)	74.4	(48.8 - 87.2)
Harefield	96	70.7	(60.4 - 78.7)	80.1	(71.2 - 86.3)
Manchester	97	86.5	(77.9 - 91.9)	85.0	(74.1 - 91.3)
Newcastle	85	81.2	(71.1 – 88.0)	79.8	(67.0 - 87.6)
Papworth	141	89.3	(82.9 - 93.4)	88.4	(80.7 - 93.0)
UK	**566**	**82.4**	**(79.0 - 85.3)**		

Centre has reached the lower 99.8% confidence limit
Centre has reached the lower 95% confidence limit
Centre has reached the upper 95% confidence limit
Centre has reached the upper 99.8% confidence limit

Table 6.4 5 year patient survival rates after first adult DBD heart transplant, by centre 1 April 2010 to 31 March 2014

Centre	Number of transplants	% 5 year survival (95% CI) Unadjusted		Risk-adjusted	
Birmingham	79	71.1	(59.3 – 80.0)	74.9	(61.8 - 83.4)
Glasgow	47	62.8	(46.9 - 75.2)	60.5	(36.5 - 75.5)
Harefield	65	73.7	(61.1 - 82.7)	65.8	(45.0 - 78.7)
Manchester	82	59.6	(48.1 - 69.3)	61.1	(45.3 - 72.4)
Newcastle	82	65.6	(54.2 - 74.8)	66.9	(52.0 - 77.1)
Papworth	119	79.8	(71.4 – 86.0)	79.3	(69.1 - 86.1)
UK	**474**	**69.7**	**(65.3 - 73.7)**		

Centre has reached the lower 99.8% confidence limit
Centre has reached the lower 95% confidence limit
Centre has reached the upper 95% confidence limit
Centre has reached the upper 99.8% confidence limit

Risk adjusted survival

The current risk adjustment model was developed by the clinical audit group in 2015. Data was obtained on 1,100 first adult isolated heart transplants performed between 1st January 2003 and 31st December 2013. Cox proportional hazard regression models were built for 30 day, 1 year and 5 year survival. Candidate variables were those chosen by the clinical audit group and those previously found to be significant in earlier risk adjustment models. Variables which reached statistical significance at the 10% level were included in the final models. Multiple imputation was used for missing values.

Adjustments were made based on feedback from the audit group and evidence of non-linear effects for some terms (spline terms were introduced). Further adjustments were made in 2016 when an interaction term between ischaemic time and the use of machine perfusion devices was introduced.

Details of the risk adjustment model are reproduced below from CTAG 16 XX.

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		1.5 (0.51, 4.42)		0.63 (0.26, 1.54)
Long-term		ECMO: 4.29 (1.49, 12.36)		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)

Risk-adjusted survival estimates are obtained through indirect standardisation. The probability of survival for each patient is determined based on their individual risk factor values. The sum of these probabilities for all patients at a centre gives the number, E, of patients or grafts expected to survive at least one year or five years after transplant at that centre. The number of patients who actually survive the given time period is given by O. The risk-adjusted estimate is then calculated by multiplying the ratio O/E by the overall unadjusted survival rate across all centres.

Issues with current risk adjustment model

1. **Out of date.** CTAG 16 XX stated that models are reviewed and updated every three years, as a minimum, to ensure they reflect current practice. The current model will be five years old in 2020.

2. **Sex-mismatching may be incorrect.** The current risk adjustment model suggests that RF:DM is associated with higher risk. However, numerous publications from other registries report that the opposite sex-mismatch RM:DF is associated with higher risk. Recent analysis using predicted heart mass equations suggests that this association is due to under-sizing.

3. **Uncertainty about discrimination and calibration.** No summary statistics presented in CTAG 16 XX.

4. **No external validation.** No process of external validation described in CTAG 16 XX.

In addition, one could argue that risk adjustment may not encourage responsible selection of recipients and donors. It is clear that recipient risk will influence post-transplant survival. Recipients at highest jeopardy such as those on short-term MCS may derive the greatest absolute gain from transplantation. However, it is also important for centres to derive an acceptable number of quality-adjusted life-years from organs that are offered for transplantation. An undesirable outcome of risk adjustment is that it could conceal the reduced survival associated with selecting high risk recipients or donor organs that may be 'higher risk' as a result of long anticipated ischaemic times.

Other risk adjustment models

Singh risk model for in hospital mortality after heart transplantation was developed from the Organ Procurement and Transplantation Network (OPTN) database.{Singh:2012fs} Data was obtained for first heart transplants between January 2007 and July 2009. The risk model was derived using multi-variable logistic regression. Models were created with recipient factors alone and with both recipient and donor factors. The recipient and donor factor model had excellent discrimination (C statistic 0.742) and calibration (Homser Lemeshow P=0.70) in the derivation cohort. It was externally validated using the OPTN database for first heart transplants between July 2009 and October 2010. It maintained reasonable discrimination (C statistic 0.695) and calibration (Homser Lemeshow P=0.42).

Table 3. Risk Prediction Model of Posttransplant In-Hospital Mortality Using Recipient and Donor Variables

Variable	Coefficient	OR	95% CI	*P*
Age at transplant				0.002
18–64 y	...	1.00	...	
≥65 y	0.6091	1.84	(1.26–2.68)	
Diagnosis				0.002
Dilated/valvular CM	...	1.00	...	
Ischemic CM/other	0.3571	1.43	(1.04–1.96)	
Hypertrophic/ restrictive CM	0.7139	2.04	(1.04–4.01)	
Congenital heart disease	1.3968	4.04	(1.86–8.79)	
Mechanical support				<0.001
ECMO	1.6930	5.44	(1.87–15.8)	
Total artificial heart/BIVAD	1.4079	4.09	(2.56–6.52)	
LVAD	0.7208	2.06	(1.44–2.94)	
None	...	1.00	...	
Ventilator	1.2825	3.61	(2.02–6.44)	<0.001
GFR				<0.001
≥60 mL/min per 1.73 m^2	...	1.00	...	
30–59 mL/min per 1.73 m^2	0.5174	1.68	(1.22–2.31)	
<30 mL/min per 1.73 m^2	0.7943	2.21	(1.17–4.18)	
Dialysis	1.3332	3.79	(2.01–7.17)	
Total serum bilirubin				0.001
<1.0 mg/dL	...	1.00	...	
1.0–2.5 mg/dL	0.2783	1.32	(0.96–1.83)	
>2.5	0.8905	2.44	(1.55–3.82)	
Donor age				0.006
<40 y	...	1.00	...	
40–54 y	0.4221	1.53	(1.10–2.11)	
≥55 y	0.8176	2.27	(1.20–4.27)	
Ischemic time				<0.001
<4.5 h	...	1.00	...	
≥4.5 h	0.6477	1.91	(1.34–2.72)	

IMPACT risk model for one-year mortality after heart transplantation was developed from the UNOS registry.{Weiss:2011jv} Data was obtained for first heart transplants between January 1997 and December 2008. The risk model was derived using multi-variable logistic regression in a random sample of 80% of the study population. This score is based solely on recipient factors and did not include donor or institutional factors. The model had reasonable discrimination (C index 0.65) and calibration (Homser Lemeshow P=0.73) in the derivation cohort. It was externally validated using the remaining 20% of the study population but summary statistics for discrimination and calibration were not presented.

Table 2. Univariate and Multivariable Logistic Regression Used to Generate Recipient Risk Score

Covariates[a]	Univariate Analysis OR (95% CI)	*p* Value	Multivariable Analysis OR (95% CI)	*p* Value[b]	Points Assigned
Age greater than 60	1.29 (1.18–1.43)	<0.001	1.35 (1.21–1.50)	<0.001	3
Bilirubin (serum)					
0–0.99	Reference		Reference		
1–1.99	1.30 (1.17–1.44)	<0.001	1.28 (1.14–1.43)	<0.001	1
2–3.99	1.70 (1.46–1.98)	<0.001	1.49 (1.27–1.75)	<0.001	3
≥4	2.12 (1.85–2.44)	<0.001	1.96 (1.68–2.29)	<0.001	4
Creatinine clearance					
>50 mL/minute	Reference		Reference		0
30–49 mL/minute	1.10 (1.00–1.22)	0.04	1.21 (1.07–1.35)	0.001	2
<30 mL/minute	2.89 (2.32–3.58)	<0.001	2.45 (1.93–3.11)	<0.001	5
Dialysis between listing and transplant	3.11 (2.46–3.94)	<0.001	1.93 (1.49–2.51)	<0.001	4
Female sex	1.18 (1.07–1.31)	0.001	1.39 (1.23–1.57)	<0.001	3
Heart failure etiology					
Ideopathic	Reference		Reference		0
Ischemic	1.26 (1.15–1.39	<0.001	1.30 (1.16–1.45)	<0.001	2
Congenital	2.57 (2.02–3.26)	<0.001	2.80 (2.15–3.65)	<0.001	5
Other	1.25 (1.06–1.47)	0.008	1.22 (1.02–1.46)	0.02	1
Infection	1.68 (1.47–1.91)	<0.001	1.33 (1.16–1.54)	<0.001	3
IABP	1.70 (1.44–2.02)	<0.001	1.26 (1.04–1.53)	0.02	3
Mechanical ventilation prior to transplant	3.69 (3.02–4.51)	<0.001	2.10 (1.66–2.67)	<0.001	5
Race					
Caucasian	Reference		Reference		
African American	1.19 (1.05–1.34)	0.005	1.36 (1.19–1.56)	<0.001	3
Hispanic	1.01 (0.84–1.21)	0.94	1.07 (0.88–1.30)	0.65	0
Other	1.08 (0.81–1.43)	0.61	0.98 (0.72–1.34)	0.90	0
Temporary circulatory support	5.42 (4.08–7.42)	<0.001	3.26 (2.35–4.53)	<0.001	7
Ventricular assist device					
Older gen pulsatile	1.34 (1.19–1.52)	<0.001	1.30 (1.14–1.50)	<0.001	3
New gen continuous (excluding HMII)	1.99 (1.07–3.69)	0.03	2.04 (1.06–3.97)	0.03	5
Heartmate II	1.07 (0.77–1.50)	0.68	1.22 (0.87–1.72)	0.25	0
Total points possible	–	–	–	–	50 points

Suggestions

1. The risk adjustment model in the UK should be reviewed.

2. **Bilirubin, recipient age, recipient gender, pre-transplant mechanical ventilation and pre-transplant renal replacement therapy should be considered for inclusion in UK risk adjustment model.** These variables are all included in the Singh and IMPACT risk scores. They are already routinely collected in the UK transplant registry.

3. **More detailed categorisation of mechanical circulatory support (MCS) should be considered for inclusion in UK risk adjustment model.** In the current risk adjustment model, the only MCS categories for 30-day survival are ECMO or no ECMO. For 1-year and 5-year survival, all forms of long-term MCS (including both implantable LVAD and TAH) are considered together.

4. **Predicted heart mass (PHM) should be considered for inclusion in UK risk adjustment model**. PHM is thought to be optimal metric for size-matching in heart transplantation. It is also thought to explain the association between sex-matching and outcomes. PHM is not collected in the UK heart transplant registry. However, PHM may be easily calculated from data that are collected in the registry (age, gender, weight, height).

5. **Pulmonary vascular resistance (PVR) should be considered for inclusion in UK risk adjustment model**. PVR is thought to be a key risk factor in heart transplantation. PVR is not included in the Singh or IMPACT risk models. PVR is not collected in the UK heart transplant registry. However, PVR may be calculated from variables that are collected in the registry (mean PA pressure, PCW pressure, cardiac output).

6. **Consideration should be given to more prominent use of unadjusted data in the annual report**.

Dr Stephen Pettit, 3rd September 2019.