NHS BLOOD AND TRANSPLANT

CARDIOTHORACIC ADVISORY GROUP

UPDATED RISK-ADJUSTED LUNG POST-TRANSPLANT SURVIVAL MODELS

SUMMARY

BACKGROUND

1. This paper presents newly developed risk adjusted lung 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 90-day, 1-year and 5-year lung post-transplant survival models.

Factor	Details
Donor CMV	Positive Negative
Donor history of smoking	No Yes
Recipient daily dose of prednisolone at registration	0 1-14 ≥15
Recipient bilirubin at registration	Continuous linear
Recipient cholesterol at registration	Continuous linear
Recipient age at transplant	Continuous non-linear
Recipient FVC at registration	Continuous linear
Ischaemia time	Continuous non-linear
Transplant type	Single lung Bilateral lung
Recipient primary disease group	COPD & emphysema CF & bronchiectasis Fibrosing lung disease Primary pulmonary hypertension Other
Transplant type*Recipient primary disease group	Interaction term
Total Lung Capacity (TLC) mismatch	Continuous linear

Jenny Mehew
Statistics and Clinical Studies **March 2016**

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BACKGROUND

1. Risk-adjusted post-transplant survival models for lung transplants are used by NHSBT in the NHS England annual organ specific report to estimate post-transplant survival at the 5 adult lung transplant centres. They are also used in the continuous monitoring of centre outcomes (CUSUMs) to determine whether centres' 90 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 lung 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 lung 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 1,412 first adult lung-only transplants performed in the UK between 1 January 2004 and 31 December 2013 were obtained from the UK Transplant Registry (UKTR). Lungs from DBD and DCD donors were included whilst heart/lung transplants were excluded.

METHODS

1. Cox proportional hazards regression models were built for 90-day, one year and five year patient survival post-transplant.

2. 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 **Appendix A**. Factors which reached statistical significance at a 10% level were included in the final models.

3. For lung retrievals involving Ex Vivo Lung Perfusion (EVLP), the definition and effect of total ischaemia time used by NHSBT (cross-clamp to reperfusion) will be different when compared to transplants where EVLP was not used. However, the Clinical Audit Group felt that the extent of this difference was not great enough to warrant excluding ishcaemia time as a factor from any of the lung models.

4. 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**.

5. 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.

6. 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

7. **Table 1** presents the twelve factors included in all three final lung models (90-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 (90-day, 1-year and 5-year) were kept in all three models.

8. **Figures 1, 2** and **3** illustrate the hazard ratios and 95% CI's for the 90-day, 1-year and 5-year models respectively.

9. Note that while transplant type and primary disease group were not significant as main effects, an interaction term between these two factors was significant and hence the main effects were included in the models. The interaction effect is illustrated in **Figures 1, 2** and **3** by comparing single lung transplants with bilateral lung transplants for each primary disease group (excluding patients with CF, bronchiectasis or Primary Pulmonary Hypertension as bilateral lung transplants are generally not performed for these patients). These figures suggest that single lung transplants for COPD & emphysema patients are associated with a lower 90 day patient survival compared with bilateral lung transplants, and that single lung transplants for patients in the 'Other' category are associated with higher 1 year patient survival compared with bilateral lung transplants.

10. **Figures 4** and **5** show the non-linear effect of recipient age upon 1-year and 5-year post-transplant survival, respectively, by illustrating how the hazard ratio changes dependent upon the value of recipient age. A horizontal line at a value of 1 would indicate no effect.

11. **Figures 6** and **7** show the non-linear effect of ischaemia time upon 1-year and 5-year post-transplant survival, respectively, by illustrating how the hazard ratio changes dependent upon the value of ischaemia time.

	Table 1: Lung model results						
		90-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						
A	CMV Positive Negative	0.06	 1.39 (0.99, 1.95) 1	0.03	 1.31 (1.03, 1.66) 1	0.001	 1.33 (1.12, 1.59) 1
B	History of smoking No Yes	0.5	 1 1.13 (0.8, 1.58)	0.55	 1 1.08 (0.85, 1.37)	0.06	 1 1.19 (0.99, 1.42)
	Recipient factors						
C	Daily dose of prednisolone at registration 0 1-14 ≥15	0.78	 1 0.95 (0.63, 1.44) 0.81 (0.45, 1.47)	0.25	 1 0.99 (0.73, 1.33) 1.35 (0.93, 1.97)	0.07	 1 1.14 (0.92, 1.42) 1.4 (1.06, 1.86)
D	Bilirubin at registration (linear)	0.01	1.03 (1.01, 1.05)	0.26	1.01 (0.99,1.03)	0.88	1.00 (0.99, 1.01)
E	Cholesterol at registration (linear)	0.04	0.84 (0.71, 1.00)	0.30	0.94 (0.84, 1.06)	0.92	1.00 (0.91, 1.08)
F	Age at transplant (non-linear)	0.19	Non-linear (non-sig)	0.01	**Figure 7**	0.0002	**Figure 8**
G	FVC at registration (linear)	0.01	0.73 (0.58, 0.92)	0.02	0.82 (0.7, 0.97)	0.16	0.92 (0.82, 1.03)
	Transplant factors						
H	Ischaemia time (non-linear)	0.27	Non-linear (non-sig)	0.06	**Figure 9**	0.01	**Figure 10**
I	Transplant type	0.79	Incorporated through J and K	0.21	Incorporated through J and K	0.49	Incorporated through J and K
J	Primary disease group For single lung transplants only; • COPD &emphysema • CF & bronchiectasis • Fibrosing lung disease • Primary pulmonary hypertension • Other	0.82	 1 1.3 (0.66, 2.55) 0.6 (0.27, 1.22) 1.7 (0.56, 5.11) 0.6 (0.23, 1.64)	0.35	 1 1.1 (0.67, 1.75) 0.8 (0.48, 1.51) 2.1 (0.93, 4.59) 0.6 (0.27, 1.35)	0.34	 1 1.0 (0.69, 1.41) 1.0 (0.69, 1.55) 1.9 (1.02, 3.43) 1.0 (0.60, 1.65)

K	Transplant type*Primary disease group interaction term Single vs bilateral; • COPD &emphysema • Fibrosing lung disease • Other	0.04	 2.1 (1.08, 4.21) 0.7 (0.37, 1.46) 0.7 (0.24, 1.74)	0.08	 1.3 (0.76, 2.14) 0.7 (0.45, 1.15) 0.5 (0.22, 1.03)	0.84	 1.2 (0.80, 1.66) 1.1 (0.76, 1.60) 1.0 (0.58, 1.59)
L	Total Lung Capacity (TLC) mismatch (linear)	0.07	1.24 (0.98, 1.56)	0.03	1.2 (1.02, 1.42)	0.02	1.16 (1.03, 1.31)

Figure 1 90-day post lung transplant survival: risk-adjusted hazard ratios and 95% confidence limits for categorical factors

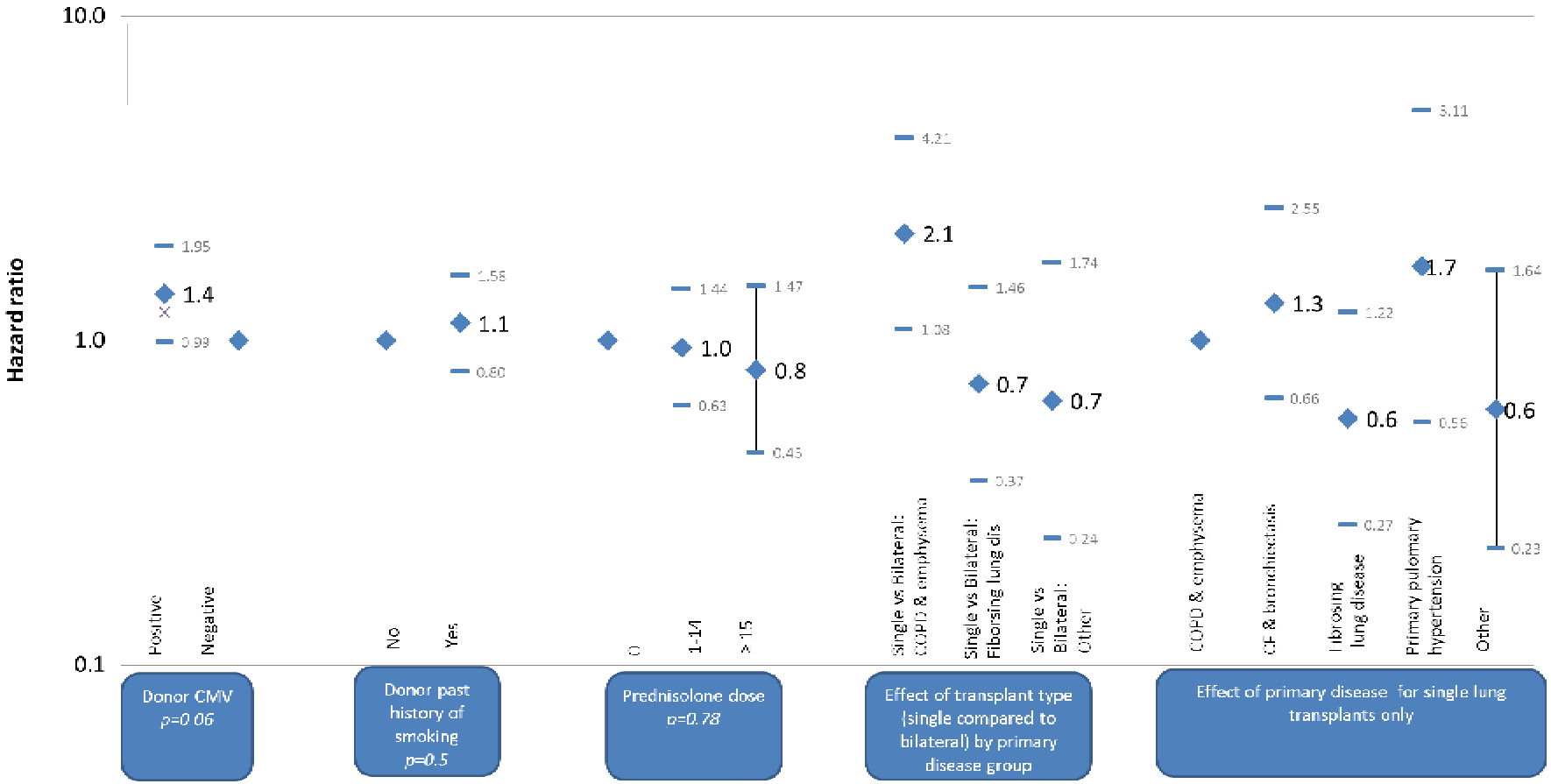


Figure 2 1-year post lung transplant survival: risk-adjusted hazard ratios and 95% confidence limits for categorical factors

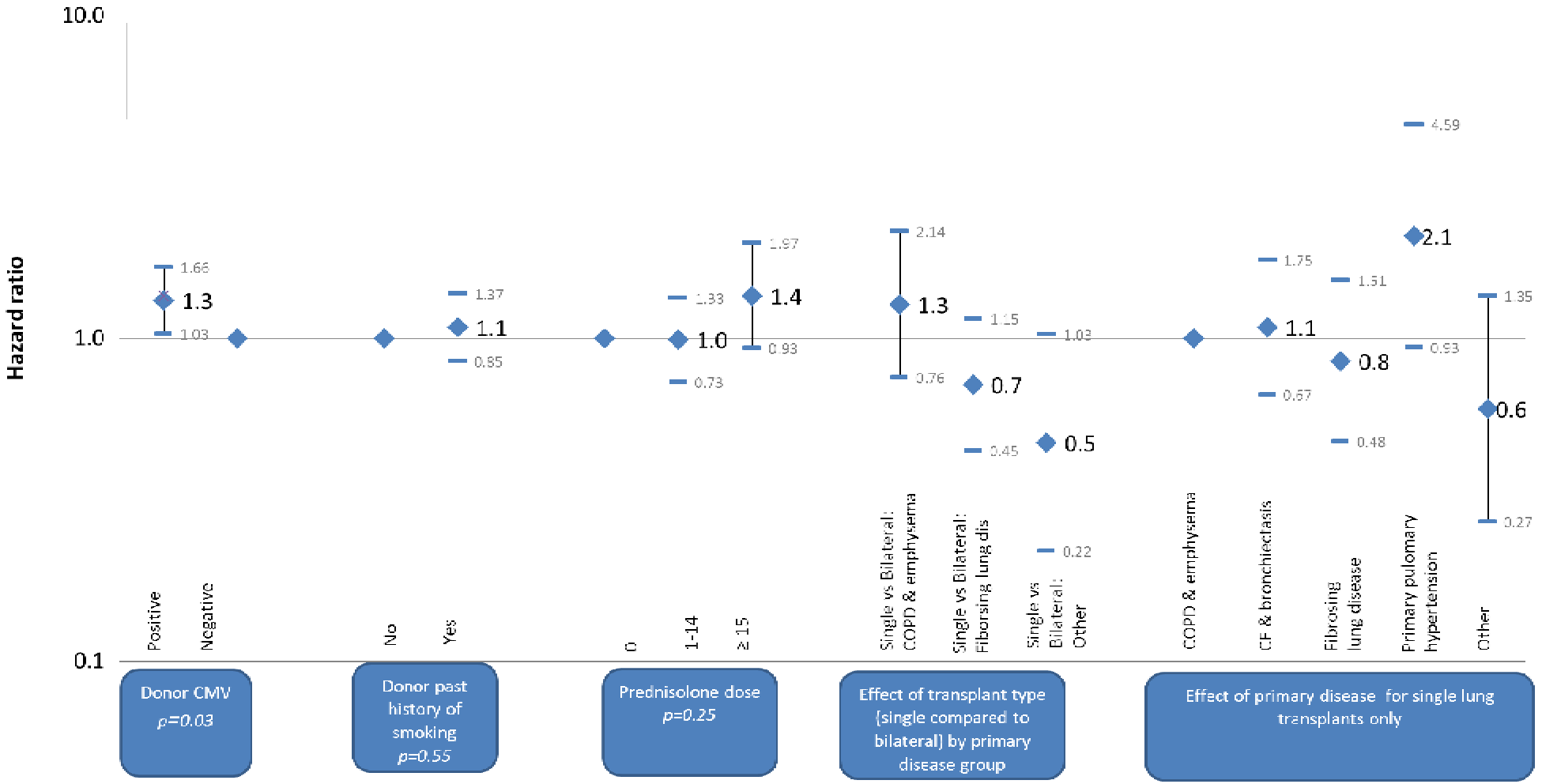


Figure 3 5-year post lung transplant survival: risk-adjusted hazard ratios and 95% confidence limits for categorical factors

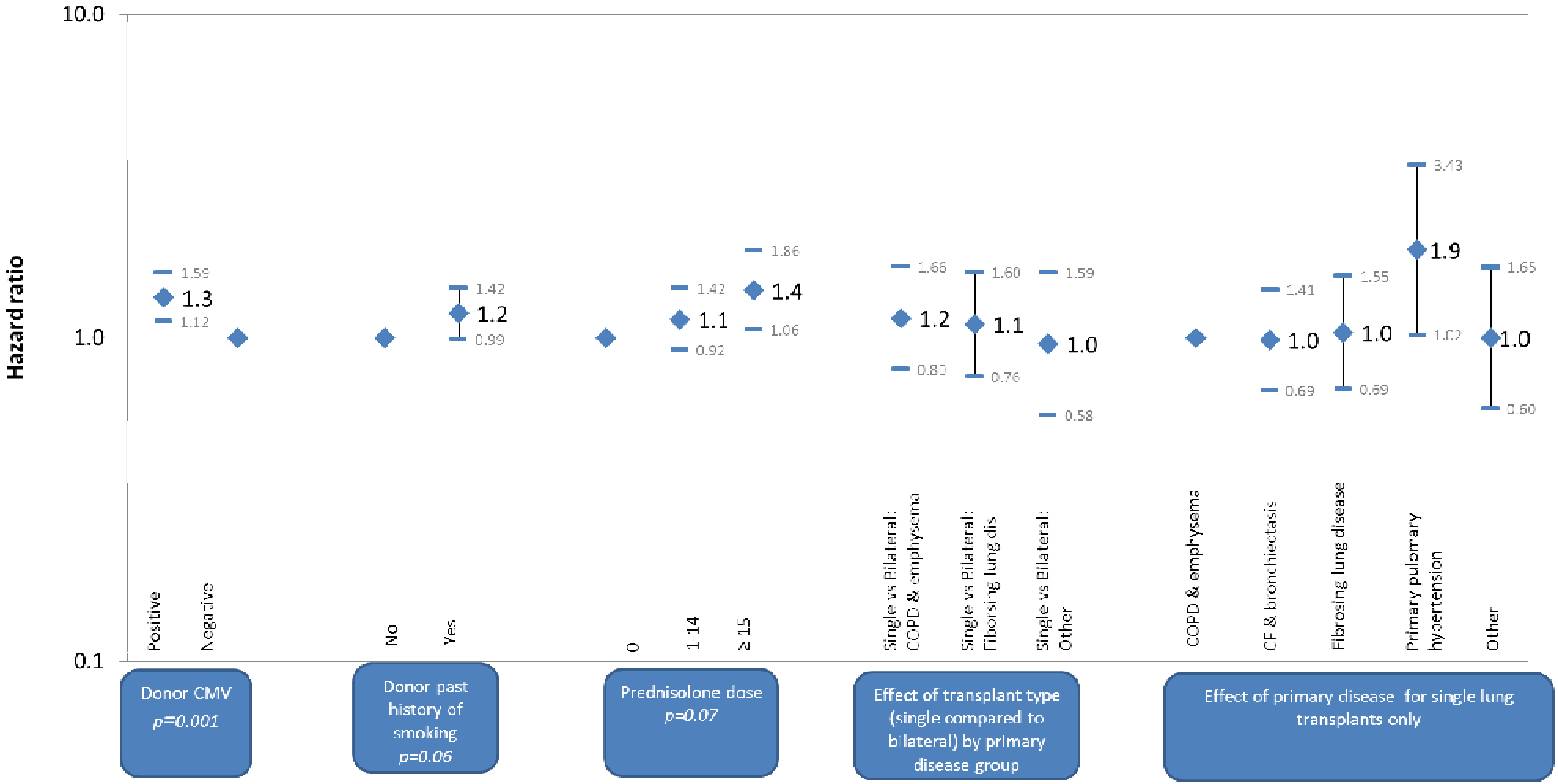


Figure 4 **1-year post lung transplant survival: risk-adjusted hazard ratio for recipient age**

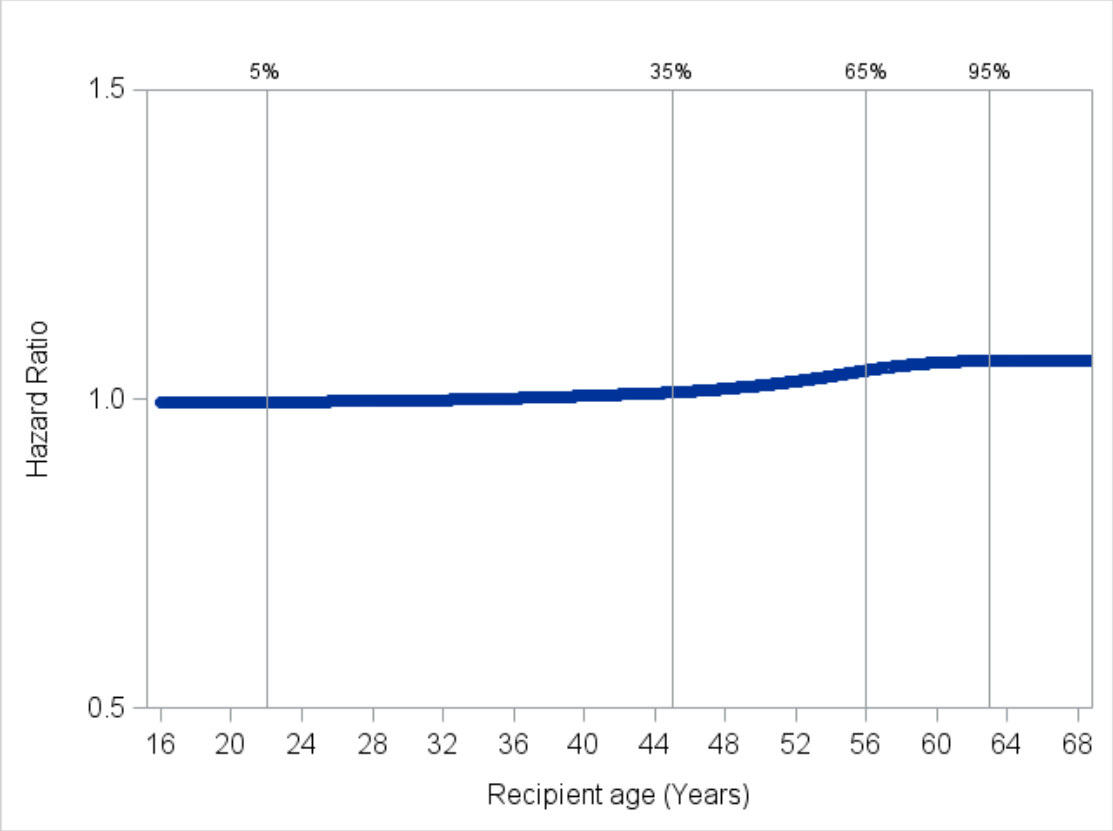


Figure 5 **5-year post lung transplant survival: risk-adjusted hazard ratio for recipient age**

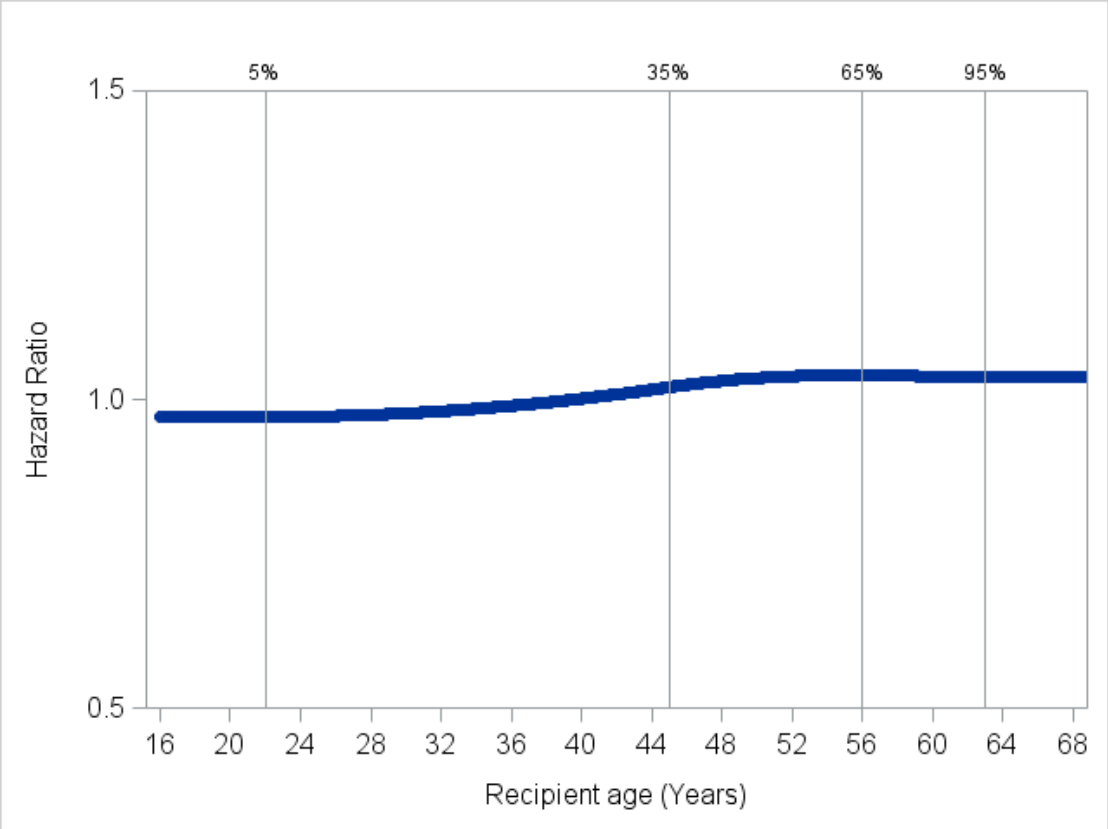


Figure 6 **1-year post lung transplant survival: risk-adjusted hazard ratio for ischaemia time**

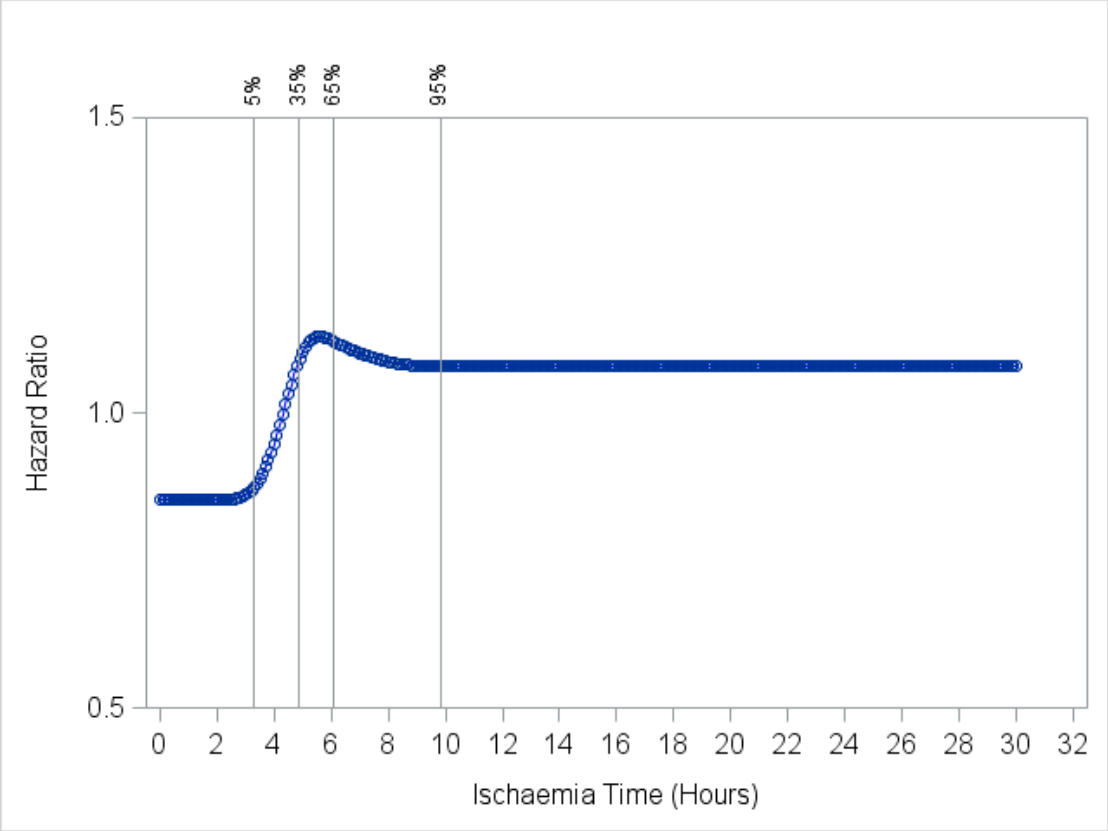
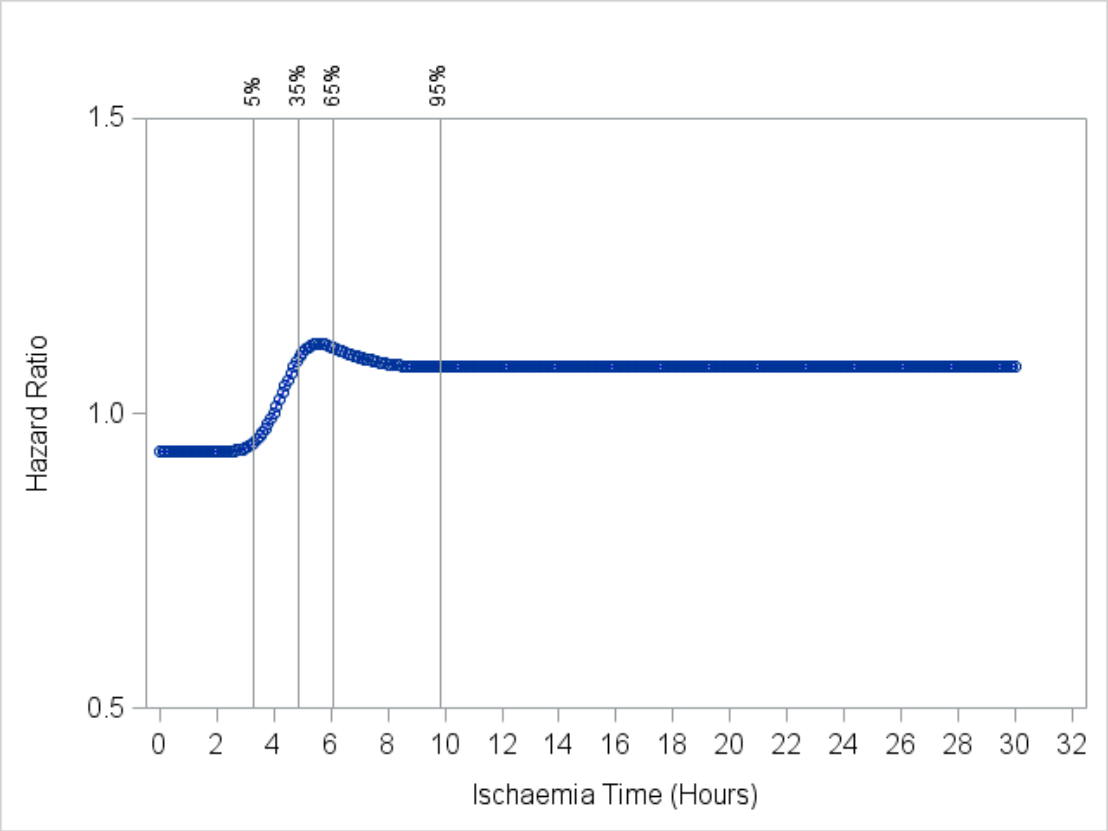


Figure 7 **5-year post lung transplant survival: risk-adjusted hazard ratio for ischaemia time**



DISCUSSION

12. 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 lung factors considered

Factor	% complete (N=1,412)	Categorisation and % observed data in each category (R=recipient, D=donor) or median (IQR) and mean (SD) for continuous factors	
Donor factors			
Donor age (years)	100%	44 (32, 52)	42 (13.5)
Donor BMI Group	99.4%	<18 (2%) 18-24 (55%)	25-29 (32%) >29 (11%)
Donor sex	100%	Male (43.1%),	female (56.9%)
History of smoking	96.7%	No (57.9%),	Yes (42.1%)
History of alcohol abuse	96.3%	No (88.3%),	Yes (11.7%)
Donor CMV	98.9%	Negative (56.8%),	positive (43.2%)
Past history of a tumour	96.4%	No (95.9%),	Yes (4.1%)
Past history of diabetes	96.6%	No (95.9%),	Yes (4.1%)
Cause of death	99.7%	Intracranial (81.8%) Trauma – RTA (5.4%)	Trauma – Other (5.6%) Other (7.2%)
Donor type	100%	DBD (90.2%)	DCD (9.8%)
Surgical factors			
CMV mismatch (-=negative, +=positive)	98.4%	R - : D - (33.3%) R +: D + (22.2%)	R - : D + (21.1%) R +: D - (23.4%)
Sex mismatch (M=male, F=female)	100%	R M : D M (38.7%) R F : D F (39.1%)	R M : D F (17.8%) R F : D M (4.4%)
Size mismatch by height (recipient – donor height)	99.4%	1 (-6, 3) cm	-1.4 (7.4)
Size mismatch by weight (recipient – donor weight)	99.7%	-5.7 (-17,5.9)	-5.5 (17.6)
Transplant type	100%	Single lung (22.7%)	Double lung (77.3%)
Perfusion fluid	91.6%	LPDS (73.6%) Other (26.4%)	
Recipient factors			
Recipient age (years)	100%	52 (38,58)	47 (13.4)
Recipient BMI group	99.9%	<18 (7.5%) 18-24 (55.8%) 25-29 (30.2%) >29 (6.5%)	

Recipient Primary Disease Group	99.7%	CF and bronchiectasis (29.7%) COPD and Emphysema (36.3%) Fibrosing Lung Disease (20.2%) Primary Pulmonary Hypertension (2.2%) Other (11.6%)	
Daily dose of prednisolone at time of registration (mg)	98.3%	Not given (64.0%) < 15 (25.2%)	≥ 15 (10.8%)
Recipient sex	100%	Male (56.5%)	Female (43.5%)
NYHA Class	99.7%	I No limitations of activities (0.8%) II Slight limitation (5.5%) III Marked limitation (82.1%) IV Confined to bed/chair (11.6%)	
6 minute walk test at registration (m)	83.9%	220 (130, 320)	235.0(126.9)
Recipient CMV	99.4%	Negative (54.1%)	Positive (45.9%)
Recipient hospitalised	99.9%	No (93.5%)	Yes (6.5%)
Infection requiring IV antibiotics within 6 weeks prior to registration	99.3%	No (73.5%)	Yes (26.5%)
Diabetes	99.9%	No (83.7%) Yes – insulin dependent (12.7%) Yes – not insulin dependent (3.6%)	
Previous thoracotomy	99.8%	No (94%)	Yes (6%)
Previous malignancy	99.8%	No (97.5%)	Yes (2.5%)
eGFR at registration	99.2%	96.2 (78.2, 120.2)	104.1 (40.3)
Cholesterol at registration (mmol/l)	95.3%	4.8 (3.8, 5.7)	4.8 (1.3)
Bilirubin at registration (µmol/l)	97.1%	9 (6, 13)	10.7 (7.2)
If in hospital, on ECMO at transplant?	99.9%	No (99.1%)	Yes (0.9%)
If in hospital, ventilated at transplant	99.9%	No (99.1%)	Yes (0.9%)
If in hospital, on inotropes at transplant	99.9%	No (99.4%)	Yes (0.6%)
FEV_1 at registration (litres)	97%	0.8 (0.57, 1.23)	1.02 (0.66)
FVC at registration (litres)	96.8%	2 (1.53, 2.56)	2.12 (0.84)