NHS BLOOD AND TRANSPLANT

LIVER ADVISORY GROUP

NATIONAL LIVER OFFERING SCHEME - UPDATING THE ESTIMATES USED TO CALCULATE THE ESTIMATED TRANSPLANT BENEFIT SCORE

METHODS PAPER

1. INTRODUCTION

1.1. The National Liver Offering Scheme (NLOS) was introduced on 20 March 2018 for donation after brain death (DBD) donors and mainly for liver offers to named adult and large paediatric patients. Offering of livers from donors after circulatory death (DCD) has not changed and remains on a centre-specific basis rather than on a patient specific basis. It was agreed prior to implementation that the estimates used to calculate the Transplant Benefit Score (TBS) would be updated on a regular basis to ensure the score accurately reflects current practice.

1.2. The impact of NLOS has been reviewed on a regular basis since March 2018 by the NLOS monitoring committee and concerns have been raised regarding the small number of named patient offers to certain patient groups (e.g. HCC).

1.3. It was agreed at the Liver Advisory Group (LAG) meeting in November 2019 that a Fixed Term Working Unit (FTWU) should be established to examine the impact of updating the estimates. The group have met regularly and members of this FTWU are:

Prof. Doug Thorburn (LAG Chair) - Royal Free Hospital, London

Mr John Isaac (Deputy LAG Chair) - Queen Elizabeth Hospital, Birmingham

Dr. Mark Hudson (NLOS monitoring committee chair) - Freeman Hospital, Newcastle

Dr. Varuna Aluvihare – King's College Hospital, London

Dr. Alex Gimson (Previous allocation FTWU Chair) - Addenbrooke's Hospital, Cambridge

Mrs Rachel Johnson - Statistics and Clinical Research, NHSBT, Bristol

Dr Ian Rowe - St James's University Hospital, Leeds

Mrs Rhiannon Taylor - Statistics and Clinical Research, NHSBT, Bristol

1.4. This paper summarises the updated analyses and simulations undertaken.

2. TRANSPLANT BENEFIT SCORE

2.1. The estimated Transplant Benefit Score (TBS) is the difference between the risk-adjusted estimated five year survival post-transplant with a specific donor (M2) and the estimated risk-adjusted five year survival on the list (M1). Blood group and weight compatible adult and large paediatric non-cancer or cancer patients are ranked by descending TBS and offered accordingly. The TBS is not used for variant syndrome patients or paediatric patients that are not dual-listed.

2.2. Survival on the transplant list (M1)

2.2.1. The currently applied survival on the transplant list model was derived from 4,827 adult elective NHS group 1 registrations for a liver only transplant in the UK between 1 January 2006 and 31 December 2012, extracted from the UK Transplant Registry on 9 June 2014. Registrations ending in living or domino donor transplantation and multi-organ registrations were excluded.

2.2.2. The cohort for the updated analysis was 8,393 adult elective NHS group 1 registrations for a liver only transplant in the UK between 1 January 2006 and 31 December 2016, extracted from the UK Transplant Registry on 12 June 2020.

2.2.3. Both the currently applied cohort and updated cohorts were split into two datasets based on whether the patient had cancer or non-cancer liver disease at time of registration. Cancer parameters that were examined for their impact on survival were maximum AFP, maximum tumor size and tumour number. Details of the M1 model for both non-cancer and cancer cases are shown in **Appendix 1**.

2.2.4. Variant syndrome patients where UKELD is not relevant or, if relevant, less than 49 (N=227) were excluded from the updated analysis along with 8 HCC downstaged patients.

2.2.5. Individual registration year is included as a factor in both the cancer and non-cancer risk-adjusted models. However, **analyses showed that the position of the baseline survivor function varied greatly depending upon the individual registration year chosen to be the baseline**. The earliest registration year (2006 for non-cancer and 2009 for cancer) were used as the baseline year in the original analysis with new registrations after 2012 allocated to the baseline year. It was agreed that this needed further exploration and that, as a principle, grouped registration year should be included in the updated analysis and that new registrations should be allocated to the latest registration year group (as intuitively that should be the group most appropriate for new registrations).

ACTION: Grouped registration year used instead of individual registration year.

2.2.6. The factors included in the currently applied models were based on either previous analyses or clinical judgement. The FTWU reviewed the many factors included in the models and agreed the principle that factors should only be included in the final, updated models if they were statistically significant in the specific cohorts.

ACTION: Factors should only be included in the four updated models (ie including M2) if statistically significant.

2.3. Multivariable analyses were performed on the updated cohort to identify the factors found to be statistically significant predictors of either survival on the list or survival post-transplant.

2.4. Full details of the cohorts, methods and models for M1 are shown in **Appendix 1**.

2.5. Survival after transplantation (M2)

2.5.1. The currently applied M2 estimates and baseline survivor function were derived from 3,484 adult elective NHS group 1 orthotopic liver only transplants in the UK between 1 January 2006 and 31 December 2012 using livers from deceased donors (both donors after brain death (DBD) and donors after circulatory death (DCD)) extracted from the UK Transplant Registry on 6 July 2014.

2.5.2. The cohort for the updated analysis was 6261 adult elective NHS group 1 orthotopic liver only transplants in the UK between 1 January 2006 and 31 December 2016 using livers from deceased donors (both DBD and DCD) were extracted from the UK Transplant Registry on 28 April 2021.

2.6. The dataset was then split into two datasets based on whether the patient had cancer or non-cancer liver disease at time of transplant. Cancer parameters that were examined for their impact on survival were maximum AFP, maximum tumor size and tumour number.

2.7. Full details of the cohorts, methods and models for M2 are shown in **Appendix 2**.

3. Simulation of liver allocation compared to current arrangements

3.1. In order to examine cohorts and baseline registration years, a total of 14 simulations were conducted and compared (in a number of iterative discussions), with the transplantation process for real historical candidates on the transplant waiting list during the first full financial year of NLOS (1 April 2018 to 31 March 2019). The final four simulations were run to try to overcome issues with unrepresentative baseline survivor functions, linked to a lack of real data beyond two years for M1 (ie few patients are still waiting for a transplant after two years on the list).

3.1.1. Real time actual patients given their organ as decided by each transplant centre during the simulation period (current arrangements) are compared with simulations shown in **Table 1**.

Table 1 Simulations run	
Simulation	**Details (M2 as current for Sims 1 – 12)**
S1	Current cohort (and models) with earliest baseline year (2006 or 2009)
S2	Current cohort with latest year as baseline (2012)
S3	Current cohort with earliest year (2006) for non-cancer and lowest baseline for cancer (2011)
S4	Updated cohort with earliest year as baseline (2006 or 2009)
S5	Updated cohort with latest year as baseline (2016)
S6	Current cohort with earliest year as baseline for non-cancer (2006) and updated cohort with earliest year as baseline for cancer (2009)
S7	Current cohort with earliest baseline year group for non-cancer (2006-2008) and no registration year for cancer
S8	Current cohort with latest baseline year group for non-cancer (2009-2012) and no registration year for cancer
S9	Updated cohort with earliest baseline year group (2006-2008 for non-cancer and 2009-2012 for cancer)
S10	Updated cohort with latest baseline year group (2013-2016 for both)
S11	Updated cohort with earliest baseline year group (2006-2008 for non-cancer and 2009-2012 for cancer) using **simulated** M1 baseline survivor functions for both cancer and non-cancer
S12	Updated cohort with latest baseline year group (2013-2016 for both) using **simulated** M1 baseline survivor functions for both cancer and non-cancer
S13	Full updated models for both M1 and M2 with latest registration year group (2013-2016) and using **simulated** M1 baseline survivor functions for both cancer and non-cancer
S14	Updated models including variables found to be statistically significant at a 10% significance level for both M1 and M2 with latest registration year group (2013-2016) and using **simulated** M1 baseline survivor functions for both cancer and non-cancer

3.2. The simulations were run assuming a single waiting list with national distribution, with DCDs excluded. The allocation of livers for all simulations required ABO compatibility and recipient weight ±20kgs of donor.

3.3. The two primary outcomes were the

3.3.1. total number of deaths or removals (because of condition deteriorating), by aetiology

3.3.2. proportion of HCC patients as the top named patient

3.3.3. the total population life years which accumulates expected survival both on the list and after transplantation.

3.4. Details of the simulation methods are given in **Appendix 3**.

SUMMARY

4. This paper summarises the methods used in an iterative series of work and discussions concerning the National Liver Offering Scheme. The accompanying results paper shows simulation results and conclusions drawn.

Rhiannon Taylor **November 2021**
Statistics & Clinical Research, NHSBT

Appendix 1

5. Survival on the transplant list – M1.

5.1. The currently applied M1 was derived from 4,827 adult elective NHS group 1 registrations for a liver only transplant in the UK between 1 January 2006 and 31 December 2012, extracted from the UK Transplant Registry on 9 June 2014. Registrations ending in living or domino donor transplantation and multi-organ registrations were excluded.

5.2. The cohort for the updated analysis was 8,393 adult elective NHS group 1 registrations for a liver only transplant in the UK between 1 January 2006 and 31 December 2016, extracted from the UK Transplant Registry on 12 June 2020.

5.3. Two explanatory variables included in M1 (renal support and patient location) were not recorded on the Elective Liver Recipient Registration form until September 2007, thus they were missing by design in around 20% of cases. Rather than moving the time period for the cohort forward from January 2006 or having missing categories for these factors and allowing M1 to estimate parameters for these levels, it was agreed that Multiple Imputation (MI; Rubin, 1987) would be used to impute the missing values.

5.4. MI was implemented in SAS 9.3, using chained equations. The form of the imputation model was exactly the same as M1 but also the outcome variables, survival time and censoring indicator, were included to aid the imputation. Other variables not in M1 that could help predict the missing values were not investigated. Twenty-one imputations were run with 50 burn-in iterations before each imputation. Instead of proceeding to run M1 21 times with different imputed datasets and obtaining 21 estimates for each parameter in the model, as is common practice, the modal value out of the 21 imputed values for each patient with missing renal support status/patient location was taken. This was because estimating 21 versions of M1 was too computationally exhaustive. Twenty-one was chosen as the number of imputations so that there would always be a modal number of zeros or ones (note that renal support status and patient location are both binary variables).

5.5. Both the currently applied cohort and updated cohorts were split into two datasets based on whether the patient had cancer or non-cancer liver disease at time of registration. Variant syndrome patients where UKELD is not relevant or, if relevant, less than 49 (N=227) were excluded from the updated analysis along with 8 HCC downstaged patients.

5.6. For the cancer cohort, information regarding the maximum AFP level and number and size of tumours was not collected until September 2007 and data was not fully reported until January 2009. Therefore, the time period for the cancer cohort was moved to include all registrations between 1 January 2009 and 31 December 2012 for the currently applied models and 1 January 2009 to 31 December 2016 for the updated models. The time period for the non-cancer cohort remained as registrations between 1 January 2006 and 31

December 2012 (currently applied) and 1 January 2006 to 31 December 2016 for the updated models.

5.7. The complete case cohorts were

5.7.1. **Current (2006-2012, 2009-2012):** 3,859 registrations for the non-cancer cohort and 660 for the cancer cohort

5.7.2. **Updated (2006-2016, 2009-2016):** 6,467 registrations for the non-cancer cohort and 1,387 for the cancer cohort.

5.8. Cox proportional hazards modelling was used to model time from registration to death on the list or removal from the list due to deteriorating condition up to five years post-registration. Registrations ending in transplantation, removal due to improved condition or registrations that had not yet ended at time of analysis were censored. Patients who survived more than five years on the list were censored at five years.

5.9. Registrations ending in transplantation are considered to be informatively censored because during the time period 2006-2016 livers were generally allocated based on need. Therefore patients who are transplanted are censored from the study when their risk of death is quite high which means that treating their time to transplant simply as non-events may result in overoptimistic survival. Inverse probability of censoring weights (IPCW) (Robins and Finkelstein, 2000) were used to account of this informative censoring. The probability of censoring was estimated from a survival model with a Weibull parameterization where informative censoring (i.e. transplantation within five years) was the event. The explanatory variables in the Weibull model were identical to those used in M1. The IPCW were then used to weight the contribution of each individual to the partial likelihood of M1 at each event time. To account for the additional uncertainty in the model specification a robust “sandwich” estimate of the covariance matrix was necessary. This led to wide confidence intervals for the resulting parameter estimates.

5.10. For both cohorts, creatinine, bilirubin, INR and maximum AFP level (for cancer cohort only) were transformed using the natural logarithm as their distributions were particularly skewed. After this transformation the distributions appeared to satisfy the normal assumption more adequately.

5.11. **Table A1 1a and A1 1b** show characteristics for both the non-cancer and cancer cohorts in the current and updated cohorts.

5.12. **Table A1 2A** and **Table A1 3A** shows the hazard ratios and p-values for each term and interactions included in the currently applied non-cancer and cancer models respectively. **Table A1 2B** and **Table A1 3B** show the equivalent models using updated cohorts.

5.13. Multivariable analyses were performed on the updated cohorts without IPCW weight and **Table A1 2C** and **Table A1 3C** show the hazard ratios and p-values for the factors found to be statistically significant predictors of survival on the list for non-cancer and cancer respectively at a 10% significance level. All but one factor (gender) as statistically significant predictors for the non-cancer while 10 of the 15 factors in the cancer model were identified as statistically significant predictors.

5.14. **Figure A1 1** shows the risk-adjusted survival curves (*baseline survivor function*s) for an average registration in the current cohort and the updated cohorts. An average registration was defined as a

5.14.1. 51 year old male with ALD registered in 2006 *(current)* or 2013-2016 (*updated*) who was not on renal replacement therapy and was an outpatient with a bilirubin of 62, creatinine of 84, INR of 1.4, sodium of 136. **(Non-cancer)**

5.14.2. 57 year old male registered in 2009 who was not on renal replacement therapy and was an outpatient with a bilirubin of 22, creatinine of 75, INR of 1.2 and sodium of 138. The cancer variable values were maximum AFP of 21, maximum tumour size of 2.6cm and only one tumour. (**cancer**)

5.15. **Figure A1 1** shows that there is a lack of data beyond two years in particular for the cancer cohort. **Figure A1 2** shows the 2.5 year post-registration outcome for cancer and non-cancer patients and shows that the majority of patients have a known outcome at 2.5 years. Other registries and known data were examined and clinically relevant baseline survival functions were estimated. This estimated survival function (labelled “Simulated”) is shown in **Figure A1 1.** It was agreed that the simulated baseline survival function should be used. **ACTION Use simulated baseline survival function with parameter estimates for statistically significant factors from updated cohort.**

5.16. The Type III test p-values convey the significance of each term at explaining the data when compared with a model that does not include the term in question. The Wald test p-values represent the significance in Hazard Ratio difference between a level and the baseline for each term in the model. Note that it is inappropriate to interpret Hazard Ratios and Wald test p-values of main effects that are included in interactions.

Table A1 1a Characteristics of registrations in the current and updated analysis (categorical variables)

	Non-cancer cohort				Cancer cohort			
	Current cohort (N=3859)		Updated cohort (N=6467)		Current cohort (N=660)		Updated cohort (N=1387)	
	N	%	N	%	N	%	N	%
Sex								
Male	2382	62	4039	62	515	78	1096	79
Female	1477	38	2428	38	145	22	291	21
Blood group								
O	1729	45	2960	46	300	45	633	46
A	1501	39	2509	39	242	37	519	37
B	476	12	771	12	80	12	170	12
AB	153	4	227	4	38	6	65	5
Ethnic origin								
White	3399	88.1	5717	88.4	542	82	1167	84
Asian	306	7.9	472	7.3	70	11	130	9
Black	82	2.1	172	2.7	19	3	33	2
East Asian	16	0.4	29	0.5	19	3	34	2
Other	56	1.5	77	1.2	10	1	23	2
Disease group								
Cancer	-	-	-	-	660	100	1387	100
Hepatitis C (HCV)	559	15	814	13	-	-	-	-
Alcoholic liver disease (ALD)	1097	28	1969	30	-	-	-	-
Hepatitis B (HBV)	79	2	128	2	-	-	-	-
Primary sclerosing cholangitis (PSC)	392	10	714	11	-	-	-	-
Primary biliary cholangitis (PBC)	402	10	616	10	-	-	-	-
Auto-immune + cryptogenic disease (AID)	384	10	604	9	-	-	-	-
Metabolic liver disease	294	8	605	9	-	-	-	-
Other liver disease	295	8	399	6	-	-	-	-
One or more previous tx	357	9	618	10	-	-	-	-
HCV								
No	3278	85	5617	87	377	57	791	57
Yes	581	15	850	13	283	43	596	43
Renal support								
No renal support	3684	96	6312	98	644	98	1368	99
Renal support	175	4	155	2	16	2	19	1
Patient location								
Outpatient	3190	83	5364	83	633	96	1345	97
Inpatient	669	17	1103	17	27	4	42	3

Registration year								
2006	474	12	474	7	-	-	-	-
2007	499	13	491	8	-	-	-	-
2008	539	14	517	8	-	-	-	-
2009	545	14	521	8	153	23	153	11
2010	576	15	561	9	170	26	169	12
2011	624	16	612	9	178	27	178	13
2012	602	16	584	9	159	24	159	11
2013	-	-	634	10	-	-	192	14
2014	-	-	720	11	-	-	193	14
2015	-	-	680	11	-	-	170	12
2016	-	-	673	10	-	-	173	12
Number of tumours								
1	-	-	-	-	448	68	939	68
2	-	-	-	-	150	23	307	22
3	-	-	-	-	43	6	103	7
4	-	-	-	-	13	2	30	2
5	-	-	-	-	6	1	8	1

Table A1 1b **Continuous characteristics of registrations in the current and updated analysis**

		Non-cancer				Cancer cohort			
		Current cohort (N=3859)		Updated cohort (N=6467)		Current cohort (N=660)		Updated cohort (N=1387)	
		Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range
Age (years)		53 (44, 59)	17 – 74	53 (44, 60)	17 - 75	58 (53, 62)	22 – 73	59 (54, 63)	19 - 73
BMI (kg/m^2)		26.0 (23.0, 30.1)	10.5 - 54.2	26.3 (23.1, 30.4)	3.1 - 60.6	27.1 (24.2, 30.6)	15.9 – 45.9	27.7 (24.6, 31.0)	3.9 - 45.9
Sodium (mmol/l)		136 (133, 139)	111 – 181	136 (133, 139)	111 - 181	139 (136, 141)	118 – 148	139 (136, 141)	118 - 148
Bilirubin (µmol/l)	Linear	57 (32, 118)	1 - 1438	57 (32, 114)	1-1438	21 (13, 34.5)	3 – 405	21 (13, 34)	3 - 405
	Logged	4.0 (3.5, 4.8)	0 – 7.3	4.0 (3.5, 4.7)	0 -7.3	3.0 (2.6, 3.5)	1.1 – 6.0	3.0 (2.6, 3.5)	1.1 – 6.0
Creatinine (µmol/l)	Linear	82 (68, 101)	7.9 – 720	79 (64, 99)	11.6 - 720	75 (64, 88)	32 – 205	74 (63, 86)	30 - 205
	Logged	4.4 (4.2, 4.6)	2.1 – 6.6	4.4 (4.2, 4.6)	2.5 - 6.6	4.3 (4.2, 4.5)	3.5 – 5.3	4.3 (4.1, 4.5)	3.4 – 5.3
INR	Linear	1.4 (1.2, 1.6)	0.1 – 9.9	1.4 (1.2, 1.7)	0.1 - 9.9	1.2 (1.1, 1.3)	0.9 – 4.9	1.2 (1.1, 1.3)	0.8 - 4.9
	Logged	0.3 (0.2, 0.5)	-2.3 – 2.3	0.3 (0.2, 0.5)	-2.3 - 2.3	0.2 (0.1, 0.3)	-0.1 – 1.6	0.2 (0.1, 0.3)	-0.2 – 1.6
Max AFP level	Linear	-	-	-	-	11 (4, 51)	0 – 9000	10 (5, 40)	1 - 9001
	Logged	-	-	-	-	2.5 (1.6, 4.0)	0 – 9.1	2.3 (1.6, 3.7)	0 - 9.1
Max tumour size	Linear	-	-	-	-	2.5 (1.9 – 3.1)	0.1 – 7.2	2.5 (1.9, 3.0)	0.1, 7.2

IQR=Inter-quartile range

Table A1 2a **Currently applied M1 non-cancer results with IPCW weights**

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III p-values
Main effects							
Age at registration	Linear	3859	0.85	0.80	0.90	<0.0001	<0.0001
	Squared	3859	1.00	1.00	1.00	<0.0001	<0.0001
Sex	Male	2382	1	-	-	-	0.4
	Female	1477	0.91	0.71	1.16	0.4	
Disease group	Hepatitis C (HCV)	559	1.98	0.21	18.89	0.6	-
	Alcoholic liver disease (ALD)	1097	1	-	-	-	
	Hepatitis B (HBV)	79	23.66	0.65	856.12	0.08	
	Primary sclerosing cholangitis (PSC)	392	0.12	0.02	1.03	0.0	
	Primary biliary cholangitis (PBC)	402	14.91	0.73	305.77	0.08	
	Auto-immune + cryptogenic disease (AID)	384	0.27	0.04	1.82	0.18	
	Metabolic liver disease	294	19.12	2.34	156.54	0.006	
	Other liver disease	295	5.14	0.87	30.35	0.07	
	One or more previous tx	357	7.31	1.10	48.55	0.04	
Bilirubin	Logged	3859	0.44	0.05	4.10	0.5	-
Creatinine	Logged	3859	2.25	1.58	3.20	<0.0001	<0.0001
INR	Logged	3859	1.57	1.07	2.32	0.02	0.02
Sodium	Linear	3859	0.89	0.83	0.97	0.007	-
Renal support	No	3684	1	-	-	-	0.9
	Yes	175	0.97	0.53	1.76	0.91	
Patient location	Outpatient	3190	1	-	-	-	0.9
	Inpatient	669	0.98	0.65	1.48	0.92	
Registration year	2006	474	1	-	-	-	<0.0001
	2007	499	0.34	0.22	0.52	<0.0001	
	2008	539	0.80	0.55	1.18	0.3	
	2009	545	0.21	0.10	0.43	<0.0001	
	2010	576	0.45	0.32	0.64	<0.0001	
	2011	624	0.47	0.33	0.68	<0.0001	
	2012	602	0.67	0.47	0.96	0.03	
Interactions							
Ln(bilirubin)* disease group	HCV	559	0.93	0.54	1.60	0.8	<0.0001
	ALD	1097	1	-	-	-	
	HBV	79	0.47	0.20	1.13	0.09	
	PSC	392	1.45	0.95	2.2	0.08	
	PBC	402	0.55	0.29	1.06	0.07	
	AID	384	1.45	0.97	2.18	0.07	
	Metabolic liver disease	294	0.53	0.32	0.88	0.014	
	Other liver disease	295	0.62	0.39	0.96	0.03	
	One or more previous transplants	357	0.68	0.45	1.01	0.06	
Ln(bilirubin)*sodium		3859	1.01	1.00	1.03	0.14	0.14

IPCW=Inverse Probability of Censoring Weights

Table A1 2B **Updated FULL M1 non-cancer results with IPCW weights**

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III p-values
Main effects							
Age at registration	Linear	6467	0.87	0.80	0.95	0.0008	0.0008
	Squared	6467	1.00	1.00	1.00	<.0001	<.0001
Sex	Male	4039	1	-	-	-	0.7
	Female	2428	1.05	0.81	1.38	0.7	
Disease group	Hepatitis C (HCV)	814	8.90	0.50	158.35	0.14	<0.0001
	Alcoholic liver disease (ALD)	1969	1	-	-	-	
	Hepatitis B (HBV)	128	8.07	0.53	123.27	0.13	
	Primary sclerosing cholangitis (PSC)	714	2.24	0.24	20.50	0.5	
	Primary biliary cholangitis (PBC)	616	5.68	0.12	266.08	0.4	
	Auto-immune + cryptogenic disease (AID)	604	0.15	0.02	1.31	0.09	
	Metabolic liver disease	605	50.94	5.87	442.11	0.0004	
	Other liver disease	399	18.33	1.25	268.79	0.03	
	One or more previous tx	618	17.94	2.69	119.81	0.003	
Creatinine	Logged	6467	2.49	1.74	3.55	<.0001	<.0001
Bilirubin	Logged	6467	62.85	2.32	1703.9	0.01	0.01
INR	Logged	6467	1.33	0.87	2.05	0.19	0.19
Sodium	Linear	6467	1.04	0.93	1.16	0.5	0.5
Renal support	No	6312	1	-	-	-	0.85
	Yes	155	0.94	0.50	1.78	0.85	
Patient location	Outpatient	5364	1	-	-	-	0.04
	Inpatient	1103	0.54	0.31	0.96	0.04	
Registration year	2006-2008	1482	0.62	0.46	0.83	0.002	0.0002
	2009-2012	2278	0.54	0.39	0.76	0.0003	
	2013-2016	2707	1	-	-	-	
Interactions							
Ln(bilirubin)* disease group	HCV	814	0.58	0.30	1.13	0.11	<0.0001
	ALD	1969	1	-	-	-	
	HBV	128	0.61	0.33	1.15	0.13	
	PSC	714	0.76	0.47	1.24	0.3	
	PBC	616	0.59	0.25	1.35	0.2	
	AID	604	1.42	0.91	2.23	0.12	
	Metabolic liver disease	605	0.37	0.22	0.64	0.0004	
	Other liver disease	399	0.43	0.24	0.78	0.006	
	One or more previous transplants	618	0.53	0.34	0.81	0.003	
Ln(bilirubin)*sodium		6467	0.98	0.95	1.00	0.06	0.06

IPCW=Inverse Probability of Censoring Weights

Table A1 2C **Updated SIGNIFICANT FACTORS ONLY M1 non-cancer results with IPCW weights**

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III p-values
Main effects							
Age at registration	Linear	6467	0.87	0.80	0.94	0.0007	0.0007
	Squared	6467	1.00	1.00	1.00	<.0001	<.0001
Disease group	Hepatitis C (HCV)	814	9.02	0.51	158.45	0.13	<.0001
	Alcoholic liver disease (ALD)	1969	1	-	-	-	
	Hepatitis B (HBV)	128	8.12	0.54	122.81	0.13	
	Primary sclerosing cholangitis (PSC)	714	2.21	0.24	20.48	0.5	
	Primary biliary cholangitis (PBC)	616	5.66	0.12	268.73	0.4	
	Auto-immune + cryptogenic disease (AID)	604	0.15	0.02	1.31	0.09	
	Metabolic liver disease	605	52.31	6.16	444.14	0.0003	
	Other liver disease	399	18.56	1.27	271.77	0.03	
	One or more previous tx	618	17.83	2.66	119.35	0.003	
Bilirubin	Logged	6467	2.45	1.72	3.51	<.0001	<.0001
Creatinine	Logged	6467	61.58	2.26	1676.4	0.01	0.015
INR	Logged	6467	1.32	0.86	2.01	0.2	0.2
Sodium	Linear	6467	1.04	0.93	1.16	0.5	0.5
Renal support	No	6312	1	-	-	-	
	Yes	155	0.94	0.49	1.78	0.8	0.8
Patient location	Outpatient	5364	1	-	-	-	0.04
	Inpatient	1103	0.55	0.31	0.97	0.04	
Registration year	2006-2008	1482	0.62	0.46	0.83	0.002	0.0002
	2009-2012	2278	0.54	0.39	0.75	0.0003	
	2013-2016	2707	1	-	-	-	
Interactions							
Ln(bilirubin)* disease group	HCV	814	0.58	0.30	1.11	0.10	<.0001
	ALD	1969	1	-	-	-	
	HBV	128	0.61	0.33	1.14	0.12	
	PSC	714	0.77	0.47	1.25	0.3	
	PBC	616	0.59	0.26	1.36	0.2	
	AID	604	1.44	0.91	2.28	0.12	
	Metabolic liver disease	605	0.37	0.22	0.64	0.0003	
	Other liver disease	399	0.43	0.24	0.78	0.006	
	One or more previous transplants	618	0.53	0.34	0.81	0.004	
Ln(bilirubin)*sodium		6467	0.98	0.95	1.0	0.06	0.06

IPCW=Inverse Probability of Censoring Weights

Table A1 3A Currently applied M1 results for cancer cohort with IPCW weights

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III test p-values
Main effects							
Age at registration	Linear	660	1.98	1.12	3.49	0.02	0.02
	Squared	660	0.99	0.99	1.00	0.02	0.02
Sex	Male	515	1	-	-	-	0.93
	Female	145	0.97	0.53	1.80	0.93	
HCV	No	377	1	-	-	-	0.2
	Yes	283	1.44	0.79	2.63	0.2	
Ln(creatinine)		660	1.14	0.33	3.86	0.8	0.8
Ln(bilirubin)		660	32639.6	5.25	$2.03x10^8$	0.02	-
Ln(INR)		660	6.06	2.55	14.38	<0.0001	<0.0001
Sodium		660	1.23	0.99	1.54	0.06	-
Renal replacement therapy	No	644	1	-	-	-	0.8
	Yes	16	1.19	0.36	3.98	0.8	
Patient location	Outpatient	633	1	-	-	-	0.7
	Inpatient	27	0.825	0.30	2.30	0.7	
Registration year	2009	153	1	-	-	-	0.009
	2010	170	1.959	0.81	4.73	0.13	
	2011	178	2.563	1.09	6.01	0.03	
	2012	159	0.713	0.21	2.41	0.6	
Ln(maximum AFP level)		660	1.083	0.92	1.27	0.3	0.3
Maximum tumour size		660	1.213	0.85	1.73	0.3	0.3
Number of tumours	1	448	1	-	-	-	0.85
	2	150	1.209	0.62	2.37	0.6	
	3 or more	62	1.013	0.38	2.72	0.98	
Interactions							
Ln(bilirubin)*sodium		660	0.93	0.87	0.99	0.03	0.03

IPCW=Inverse Probability of Censoring Weights

Table A1 3B Updated FULL M1 cancer results with IPCW weights

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III test p-values
Main effects							
Age at registration	Linear	1387	1.26	0.94	1.70	0.13	0.13
	Squared	1387	1.00	1.00	1.00	0.2	0.2
Sex	Male	1096	1	-	-	-	0.4
	Female	291	1.22	0.78	1.91	0.4	
HCV	No	791	1	-	-	-	0.4
	Yes	596	0.75	0.39	1.42	0.4	
Ln(creatinine)		1387	1.52	0.51	4.55	0.5	0.5
Ln(bilirubin)		1387	2197.92	0.25	19044997	0.1	0.1
Ln(INR)		1387	4.47	2.05	9.74	0.0002	0.0002
Sodium		1387	1.23	0.98	1.53	0.07	0.07
Renal replacement therapy	No	1368	1	-	-	-	0.2
	Yes	19	2.18	0.63	7.52	0.2	
Patient location	Outpatient	1345	1	-	-	-	0.7
	Inpatient	42	0.84	0.37	1.92	0.7	
Registration year	2009-2012	659	1.39	0.73	2.67	0.3	0.3
	2013-2016	728	1	-	-	-	
Ln(maximum AFP level)		1387	1.05	0.95	1.15	0.4	
Maximum tumour size		1387	1.03	0.79	1.34	0.8	0.8
Number of tumours	1	939	1	-	-	-	0.8
	2	307	1.21	0.65	2.26	0.5	
	3 or more	141	1.31	0.38	4.57	0.7	
Interactions							
Ln(bilirubin)*sodium		1387	0.95	0.89	1.01	0.11	0.11

IPCW=Inverse Probability of Censoring Weights

Table A1 3C Updated significant factors M1 results for cancer cohort with IPCW weights

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III test p-values
Main effects							
Age at registration	Linear	1387	1.20	0.89	1.62	0.2	0.2
	Squared	1387	1.00	1.00	1.00	0.4	0.4
Ln(creatinine)		1387	1.57	0.54	4.57	0.4	0.4
Ln(bilirubin)		1387	3746.62	0.75	1868640	0.06	0.06
Ln(INR)		1387	5.04	2.29	11.06	<.0001	<0.0001
Sodium		1387	1.23	0.98	1.53	0.07	0.07
Registration year	2009-2012	659	1.48	0.75	2.90	0.3	0.3
	2013-2016	728	1	-	-	-	
Ln(maximum AFP level)		1387	1.03	0.94	1.13	0.6	0.6
Maximum tumour size		1387	1.01	0.77	1.33	0.9	0.93
Interactions							
Ln(bilirubin)*sodium		1387	0.94	0.89	1.01	0.07	0.07

IPCW=Inverse Probability of Censoring Weights

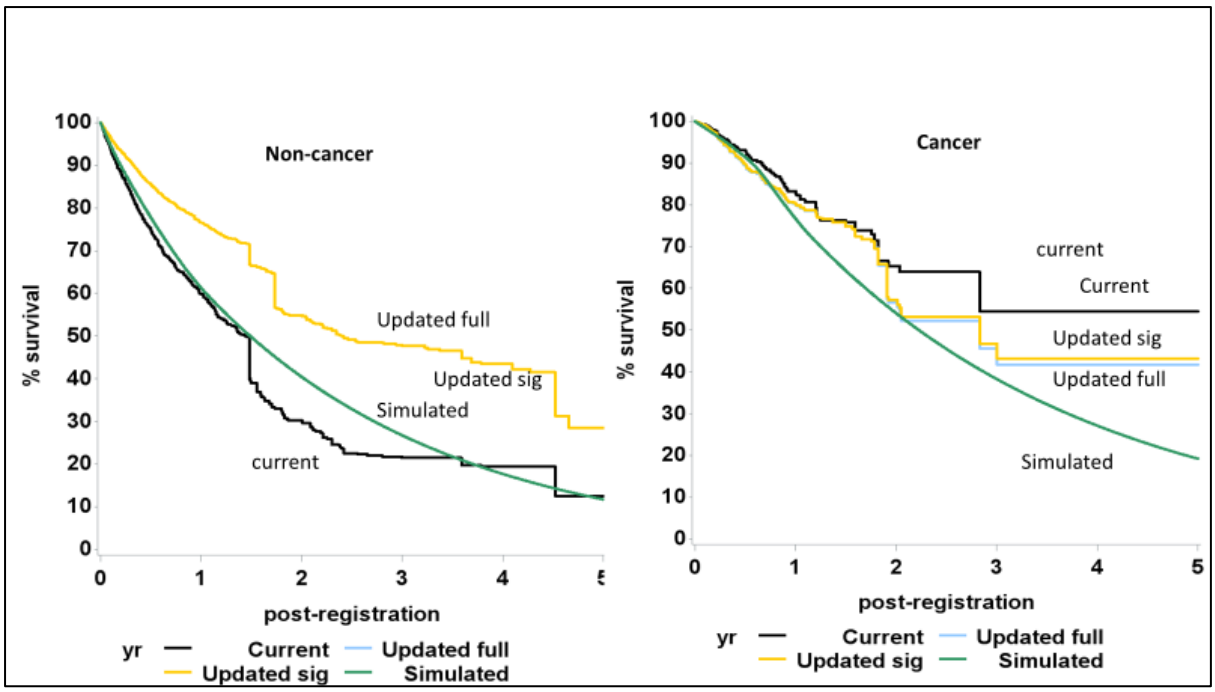

Figure A1 1 Risk-adjusted survival for an average registration in the current and updated cohorts.

Figure A1 2 two and a half year post-registration outcome for adult elective patients registered on the UK liver only transplant list

Appendix 2

6. Survival post-transplant to five years - M2

6.1. The currently applied M2 was derived from 3,484 adult elective NHS group 1 orthotopic liver only transplants in the UK between 1 January 2006 and 31 December 2012 using livers from deceased donors (both DBD and DCD) were extracted from the UK Transplant Registry on 6 July 2014.

6.2. The cohort for the updated analysis was 6261 adult elective NHS group 1 orthotopic liver only transplants in the UK between 1 January 2006 and 31 December 2016 using livers from deceased donors (both DBD and DCD) were extracted from the UK Transplant Registry on 28 April 2021.

6.3. The dataset was then split into two datasets based on whether the patient had cancer or non-cancer liver disease at time of transplant. Variant syndrome patients where UKELD is not relevant or, if relevant, less than 49 (N=140) were excluded from the updated analysis along with 5 HCC downstaged patients.

6.4. For the cancer cohort, information regarding the maximum AFP level and number and size of tumours at registration was not collected until September 2007 and data was not fully reported until January 2009. Therefore, the time period for the cancer cohort was moved to include all transplants between 1 January 2009 and 31 December 2012 for the current models and 1 January 2009 to 31 December 2016 for the updated cohort. The time period for the non-cancer cohort remained as transplants between 1 January 2006 and 31 December 2012 for the current models and 1 January 2016 to 31 December 2016 for the updated models.

6.5. One explanatory variable included in M2 (diabetes) were not recorded on the Elective Liver Recipient Registration form until September 2007 and was missing by design in around 26% of cases. Rather than moving the time period for the cohort forward from January 2006 or having a missing category for diabetes and allowing M2 to estimate parameters for these levels, it was agreed that MI would be used to impute the missing values for the whole cohort and then split into non-cancer and cancer cohorts, similar to M1.

6.6. MI for diabetes was implemented in the same manner as described in Appendix 1. However as opposed to the imputation model for M1, a binary logistic regression model was fitted to determine the variables to include in the imputation model, using the recipient variables included in M2 and blood group, ethnic origin and body mass index (BMI). Variable selection was done using stepwise selection. The statistically significant variables, at the 10% level, included in the imputation model, along with recipient diabetes, survival time and censoring indicator, were:

Recipient
Disease group
Age
Bilirubin (logged)
Potassium
Ascites
BMI
HCV
Ethnic group

Interactions
Age Bilirubin (logged)*
Age Ascites*
*Bilirubin (logged)*BMI*
Disease group Bilirubin (logged)*
Disease group Potassium*

6.7. The complete case cohorts were

6.7.1. **Current (2006-2012, 2009-2012):** 2,495 transplants for the non-cancer cohort and 430 for the cancer cohort

6.7.2. **Updated (2006-2016, 2009-2016):** 4,481 registrations for the non-cancer cohort and 1033 for the cancer cohort.

6.8. Cox proportional hazards model was used to model time from transplant to the earlier of patient death or graft failure, up to five years post-transplant (M2). Deaths with a functioning graft were included as events, whilst patients who were alive with a functioning graft were censored at date of last follow-up.

6.9. Creatinine, bilirubin, INR and maximum AFP level (for cancer cohort only) were transformed using the natural logarithm as their distributions were particularly skewed. After this transformation the distributions appeared to satisfy the normal assumption more adequately.

6.10. **Tables A2 1a-1e** show the recipient, donor and transplant characteristics, separately, for the non-cancer and cancer cohorts.

6.11. **Table A2 2A** and **Table A2 3A** shows the hazard ratios and 95% confidence intervals (CIs) for each term included in the currently applied M2 for the non-cancer and the cancer, respectively. **Table A2 2B** and **Table A2 3B** show the equivalent results for the updated cohort. Care should be taken when interpreting the hazard ratios for main effects that are involved in an interaction. Also, care should be taken in interpreting the hazard ratios for terms that have a small number of observations.

6.12. Multivariable analyses were performed on the updated cohorts and **Table A2 2C** and **Table A2 3C** show the hazard ratios and p-values for the factors found to be statistically significant, at a 10% significance level, predictors of survival on the list for non-cancer and cancer. Fifteen of the 33 factors were identified as statistically significant predictors for the non-cancer cohort while 8 of the 32 factors in the cancer model were identified as statistically significant predictors.

6.13. **Table A2 4** shows the Gonen and Heller Concordance probability and 95% confidence interval for the current and updated models.

6.14. **Figure A2 1** shows the risk-adjusted survival curves (*baseline survivor function*s) for an average registration in the current cohort and the updated cohorts. An average registration was defined as a

6.14.1. 50 year old male with ALD and no HCV who had ascites but was an outpatient, not on renal replacement therapy and did not have encephalopathy or diabetes with a bilirubin of 68, creatinine of 87, INR of 1.5, sodium of 136, potassium of 4.2, albumin of 31 and had been on the list for 77 days. The donor characteristics were a blood group identical whole liver DBD donor, aged 46 years, CVA as cause of death with a BMI of 25.9 and no history diabetes **(Non-cancer)**

6.14.2. 57 year old male without HCV who was an outpatient, not on renal replacement therapy and did not have encephalopathy, ascites or diabetes with a bilirubin of 22, creatinine of 79, INR of 1.3, sodium of 139, potassium of 4.2, albumin of 34.8 and had been on the list for 68 days. The cancer variable values were maximum AFP of 20, maximum tumour size of 2.6cm and only one tumour. The donor characteristics were a blood group identical whole liver DBD donor, aged 49 years, CVA as cause of death with a BMI of 26.4 and no history diabetes (**cancer**)

Table A2 1a Characteristics of transplants in the current and updated analysis (categorical variables)

	Non-cancer cohort				Cancer cohort			
	Current cohort (N=2495)		Updated cohort (N=4481)		Current cohort (N=430)		Updated cohort (N=1033)	
	N	%	N	%	N	%	N	%
RECIPIENT								
Sex								
Male	1505	60	2765	62	345	80	831	80
Female	990	40	1716	38	85	20	202	20
Blood group								
O	1016	41	1884	42	181	42	428	41
A	1094	44	1924	43	171	40	429	42
B	268	11	483	11	50	12	123	12
AB	117	5	190	4	28	7	53	5
Ethnic origin								
White	2214	89	3974	89	354	82	865	84
Asian	205	8	340	8	45	11	96	9
Black	45	2	106	2	15	4	29	3
East Asian	5	0.2	16	0.4	13	3	29	3
Other	26	1	45	1	3	1	14	1
Disease group								
Cancer	-	-	-	-	430	100	1033	100
Hepatitis C (HCV)	349	14	538	12	-	-	-	-
Alcoholic liver disease (ALD)	692	28	1321	29	-	-	-	-
Hepatitis B (HBV)	39	2	77	2	-	-	-	-
Primary sclerosing cholangitis (PSC)	309	12	590	13	-	-	-	-
Primary biliary cholangitis (PBC)	310	12	504	11	-	-	-	-
Auto-immune + cryptogenic disease (AID)	221	9	387	9	-	-	-	-
Metabolic liver disease	166	7	383	9	-	-	-	-
Other liver disease	199	8	281	6	-	-	-	-
One or more previous tx	210	8	400	9	-	-	-	-
HCV								
No	2142	86	3932	88	240	56	565	55
Yes	353	14	549	12	190	44	468	45
Renal support								
No renal support	2360	95	4238	95	413	96	987	96
Renal support	135	5	243	5	17	4	46	4
Patient location								
Outpatient	1958	78.5	3570	80	413	96	994	96
Inpatient	537	21.5	911	20	17	4	39	4
Previous abdominal surgery								
No previous abdominal surgery	2002	80	3621	81	383	89	927	90
Previous abdominal surgery	493	20	860	19	47	11	106	10

Encephalopathy								
No encephalopathy	1684	67.5	2965	66	389	90.5	904	88
Encephalopathy	811	32.5	1516	34	41	9.5	129	12
Ascites								
No ascites	1036	41.5	1782	30	328	76	758	73
Ascites	1459	58.5	2699	60	102	24	275	27
Diabetes								
No	2098	84	3647	81	312	73	717	69
Yes	397	16	834	19	118	27	316	31
Number of tumours								
1	-	-	-	-	283	66	686	66
2	-	-	-	-	100	23	229	22
3	-	-	-	-	31	7	87	8
4	-	-	-	-	9	2	22	2
5	-	-	-	-	7	2	9	1
DONOR								
Donor type								
Donors after brain death (DBD)	2138	86	3681	82	311	72	678	66
Donors after circulatory death (DCD)	357	14	800	18	119	28	355	34
Blood group								
O	1026	41	1901	42	183	43	431	42
A	1115	45	1962	44	177	41	441	43
B	259	10	469	10	48	11	120	12
AB	95	4	149	3	22	5	41	4
Donor cause of death								
Intracranial haemorrhage (CVA)	1675	67	2903	65	285	66	647	62
Road Traffic Accident (RTA)	177	7	241	5	14	3	48	5
Other trauma	111	4	175	4	17	4.0	36	3
Miscellaneous	532	21	1162	26	114	27	302	29
Past diabetes								
No history of diabetes	2286	92	4119	92	392	91	919	89
History of diabetes	124	5	253	6	23	5	81	8
Unknown history diabetes	85	3	109	2	15	4	33	3
TRANSPLANT								
Donor-recipient blood group compatibility								
Identical	2463	99	4419	99	422	98	1016	98
Compatible	32	1	60	1	8	2	16	2
Incompatible	0	0	2	0	0	0	1	0.1
Liver split								
Whole	2250	90	4087	91	396	92	976	94
Split	245	10	394	9	34	8	57	6

Table A2 1b Continuous characteristics of transplants in the current and updated M2 analysis

		Non-cancer				Cancer cohort			
		Current cohort (N=2495)		Updated cohort (N=4481)		Current cohort (N=430)		Updated cohort (N=1033)	
		Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range
RECIPIENT									
Age (years)		53 (44, 59)	17 - 74	53 (44, 60)	17 - 75	58 (53, 63)	23 – 72	59 (54, 64)	23 - 74
BMI (kg/m^2)		25.8 (22.9, 29.8)	11.1 - 48.2	26.0 (23,1, 34.0)	3.1 - 50.7	26.9 (24.1, 30.2)	17.3 - 45.9	27.5 (24.6, 30.8)	12.1 - 45.9
Sodium (mmol/l)		137 (133,140)	115 - 155	137 (133,140)	115 - 160	139 (137, 142)	122 - 158	139 (137, 141)	121 - 158
Potassium		4.2 (3.8, 4.5)	2.1 - 6.7	4.2 (3.9, 4.6)	2.1 - 6.7	4.1 (3.9, 4.4)	3-6.9	4.2 (3.9, 4.4)	3 - 6.9
Albumin		30 (26, 35)	10 - 61	30 (26, 34)	1 - 61	36 (30, 40)	4-51	35 (29, 40)	4 - 69
Bilirubin (µmol/l)	Linear	62 (33, 135)	2 - 1118	62 (35, 132)	2 - 1118	20 (12, 38)	4-657	22 (13, 39)	2 - 657
	Logged	4.13 (3.5, 4.91)	0.69 - 7.02	4.13 (3.56, 4.88)	0.69 - 7.02	3 (2.48, 3.64)	1.39-6.49	3.1 (2.6, 3.7)	0.7 - 6.5
Creatinine (µmol/l)	Linear	85 (70, 107)	20 - 613	81 (65, 103)	16 - 755	78 (67, 92)	33-271	76 (65, 91)	31 - 295
	Logged	4.44 (4.25, 4.67)	3 - 6.42	4.39 (4.17, 4.63)	2.77 - 6.63	4.36 (4.20, 4.52)	3.50-5.60	4.3 (4.2, 4.5)	3.4-5.7
INR	Linear	1.4 (1.2, 1.7)	0.7-10	1.5 (1.3, 1.8)	0.7-10	1.2 (1.1, 1.4)	0.9 – 3.8	1.2 (1.1, 1.5)	0.8 - 4.3
	Logged	0.34 (0.18, 0.53)	-0.36 - 2.3	0.41 (0.26, 0.59)	-0.36 - 2.3	0.18 (0.10, 0.34)	-0.11 - 1.34	0.2 (0.1, 0.4)	-0.2 - 1.5
Waiting time to transplant	Linear	95 (32, 216)	0 - 1473	89 (30, 211)	0 - 2425	72 (35, 156)	0-835	82 (37, 177)	0 - 1026
	Logged	4.56 (3.5, 5.38)	0 - 7.3	4.50 (3.43, 5.36)	0 - 7.8	4.29 (3.58, 5.06)	0-6.73	4.4 (3.6, 5.2)	0 - 6.9
Max AFP level	Linear	-	-	-	-	12 (4, 51)	0 – 9000	10 (4, 39)	0 – 9000
	Logged	-	-	-	-	2.56 (1.61, 3.95)	0 – 9.11	2.4 (1.6, 3.7)	0 – 9.1
Max tumour size	Linear	-	-	-	-	2.5 (1.9, 3.0)	0.1 – 7.0	2.5 (1.9, 3.0)	0.1 – 7.0

IQR=Inter-quartile range

Table A2 1b Continuous characteristics of transplants in the current and updated M2 analysis

	Non-cancer				Cancer cohort			
	Current cohort (N=2495)		Updated cohort (N=4481)		Current cohort (N=430)		Updated cohort (N=1033)	
	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range
DONOR								
Age (years)	48 (36, 59)	10-85	50 (37, 60)	7-86	50 (39, 61)	14 - 85	51 (30, 62)	12 - 85
BMI (kg/m^2)	25.4 (22.8, 28.3)	12.6-52.9	25.5 (22.9, 28.4)	12.6-52.9	25.6 (23.1, 28.9)	14.3-49.1	25.8 (23.1, 28.9)	14.3 - 53.3

IQR=Inter-quartile range

Table A2 2A **Currently applied M2 results for non-cancer cohort**

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III p-values
Recipient							
Age at transplant		2495	0.91	0.83	0.99	0.03	-
Sex	Male	1505	1	-	-	-	0.96
	Female	990	1.00	0.81	1.23	0.96	
Disease group	HCV	349	0.79	0.07	9.37	0.8	-
	ALD	692	1	-	-	-	
	HBV	39	13.18	0.48	361.68	0.13	
	PSC	309	0.90	0.18	4.52	0.9	
	PBC	310	0.23	0.03	2.14	0.2	
	AID	221	0.92	0.15	5.52	0.93	
	Metabolic liver disease	166	2.27	0.30	16.85	0.4	
	Other liver disease	199	1.15	0.23	5.89	0.9	
	One or more previous transplant	210	1.79	0.36	8.89	0.5	
HCV indicator	No	2142	1	-	-	-	-
	Yes	353	0.74	0.14	4.09	0.7	
Ln(creatinine)		2495	0.38	0.14	1.01	0.05	-
Ln(bilirubin)		2495	1.04	0.93	1.15	0.5	0.5
Ln(INR)		2495	0.64	0.44	0.95	0.03	0.03
Sodium		2495	0.99	0.97	1.01	0.4	0.4
Potassium		2495	1.01	0.86	1.20	0.9	0.88
Albumin		2495	0.99	0.97	1.00	0.05	0.05
Renal replacement therapy	No	2360	1	-	-	-	0.0003
	Yes	135	1.82	1.31	2.51	0.0003	
Patient location	Outpatient	1958	1	-	-	-	0.02
	Inpatient	537	1.32	1.04	1.67	0.02	
Previous abdominal surgery	No	2002	1	-	-	-	0.3
	Yes	493	1.16	0.87	1.53	0.3	
Encephalopathy	No	1684	1	-	-	-	0.93
	Yes	811	1.01	0.82	1.24	0.93	
Ascites	No	1036	1	-	-	-	0.8
	Yes	1459	1.03	0.84	1.26	0.8	
Ln(waiting time)		2495	1.00	0.93	1.07	0.93	0.93
Diabetes	No	2098	1	-	-	-	0.3
	Yes	397	1.15	0.90	1.48	0.3	

Donor							
Donor age		2495	1.01	1.00	1.01	0.09	
Donor cause of death	CVA	1675	1	-	-	-	0.2
	RTA	177	1.27	0.90	1.80	0.2	
	Other trauma	111	0.71	0.43	1.18	0.2	
	Other	532	0.93	0.73	1.18	0.6	
History of diabetes	No	2286	1	-	-	-	
	Yes	124	0.79	0.48	1.32	0.4	
	Unknown	85	1.11	0.66	1.86	0.7	
Donor BMI		2495	1.01	0.99	1.03	0.3	0.3
Donor type	DBD	2138	1	-	-	-	
	DCD	357	39.88	1.21	1309.22	0.04	
Transplant							
Blood group compatibility	Identical	2463	1	-	-	-	0.7
	Compatible	32	1.18	0.56	2.48	0.7	
Liver split	Whole	2250	1	-	-	-	0.03
	Split	245	1.43	1.03	2.00	0.03	
Interactions							
HCV*donor diabetes	No HCV or no diabetes	2467	1	-	-	-	0.07
	HCV and diabetes	17	2.32	0.86	6.25	0.1	
	HCV and unknown diabetes	11	2.47	0.86	7.14	0.09	
HCV*donor age	No	2142	1	-	-	-	0.10
	Yes	353	1.02	1.00	1.03	0.1	
Recipient age*disease group	HCV	349	1.00	0.96	1.04	0.96	0.6
	ALD	692	1	-	-	-	
	HBV	39	0.94	0.87	1.02	0.14	
	PSC	309	1.01	0.98	1.04	0.6	
	PBC	310	1.03	0.99	1.07	0.2	
	AID	221	1.00	0.97	1.04	0.94	
	Metabolic liver disease	166	0.99	0.95	1.03	0.5	
	Other liver disease	199	1.00	0.97	1.03	0.94	
	Retransplant	210	1.00	0.97	1.03	0.98	
Recipient age*ln(creatinine)		2495	1.02	1.00	1.04	0.03	0.03
Donor type *disease group	DBD or ALD	2259	1.00	-	-	-	0.8
	DCD and HCV	66	0.77	0.36	1.63	0.5	
	DCD and HBV	7	0.68	0.07	6.59	0.7	
	DCD and PSC	31	1.09	0.49	2.42	0.84	
	DCD and PBC	56	0.78	0.34	1.79	0.6	
	DCD and AID	26	0.48	0.13	1.74	0.3	
	DCD and Metabolic	25	1.52	0.60	3.81	0.4	
	DCD and other disease	22	0.50	0.14	1.85	0.3	
	DCD and retransplant	3	0.66	0.07	5.86	0.7	
Donor type*recipient age	DBD	2138	1.00	-	-	-	0.6
	DCD	357	1.01	0.98	1.03	0.6	
Donor type*ln(creatinine)	DBD	2138	1.00	-	-	-	0.04
	DCD	357	0.45	0.21	0.97	0.04	

Table A2 2B **Updated FULL M2 non-cancer results**

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III p-values
Recipient							
Age at transplant		4481	0.92	0.87	0.98	0.007	-
Sex	Male	2765	1	-	-	-	
	Female	1716	0.98	0.85	1.13	0.8	0.8
Disease group	HCV	538	0.70	0.11	4.48	0.7	-
	ALD	1321	1	-	-	-	
	HBV	77	0.95	0.09	9.51	0.96	
	PSC	590	1.06	0.36	3.12	0.91	
	PBC	504	0.24	0.05	1.27	0.09	
	AID	387	1.29	0.40	4.24	0.7	
	Metabolic liver disease	383	1.44	0.33	6.21	0.6	
	Other liver disease	281	1.42	0.44	4.55	0.6	
	Retransplant	400	3.27	1.10	9.73	0.03	
HCV indicator	No	3932	1	-	-	-	-
	Yes	549	1.15	0.32	4.08	0.8	
Ln(creatinine)		4481	0.58	0.30	1.13	0.11	-
Ln(bilirubin)		4481	0.98	0.91	1.06	0.6	0.6
Ln(INR)		4481	0.93	0.72	1.21	0.6	0.6
Sodium		4481	0.99	0.98	1.01	0.3	0.3
Potassium		4481	0.98	0.87	1.11	0.7	0.7
Albumin		4481	1.00	0.99	1.01	0.5	0.5
Renal replacement therapy	No	4238	1	-	-	-	0.07
	Yes	243	1.27	0.98	1.65	0.07	
Patient location	Outpatient	3570	1	-	-	-	0.03
	Inpatient	911	1.21	1.02	1.43	0.03	
Previous abdominal surgery	No	3621	1	-	-	-	0.06
	Yes	860	1.22	0.99	1.49	0.06	
Encephalopathy	No	2965	1	-	-	-	0.6
	Yes	1516	1.04	0.90	1.20	0.6	
Ascites	No	1782	1	-	-	-	0.9
	Yes	2699	0.99	0.86	1.15	0.9	
Ln(waiting time)		4481	1.01	0.96	1.06	0.7	0.7
Diabetes	No	3647	1	-	-	-	0.4
	Yes	834	0.93	0.78	1.10	0.4	
Donor							
Donor age		4481	1.01	1.00	1.01	0.0008	0.0008

Donor cause of death	CVA	2903	1	-	-	-	0.06
	RTA	241	1.24	0.93	1.65	0.15	
	Other trauma	175	0.93	0.66	1.30	0.7	
	Other	1162	0.85	0.73	1.00	0.06	
History of diabetes	No	4119	1	-	-	-	-
	Yes	253	1.25	0.95	1.65	0.11	
	Unknown	109	0.81	0.50	1.30	0.4	
Donor BMI		4481	1.01	0.99	1.02	0.3	0.3
Donor type	DBD	3861	1	-	-	-	-
	DCD	800	73.88	9.56	571.22	<.0001	
Transplant							
Blood group compatibility	Identical	4419	1	-	-	-	0.5
	Compatible	62	0.80	0.45	1.44	0.5	
Liver split	Whole	4087	1	-	-	-	0.04
	Split	394	1.32	1.01	1.71	0.04	
Interactions							
HCV*donor diabetes	No HCV or no diabetes	4440	1	-	-	-	0.013
	HCV and diabetes	29	1.28	0.61	2.69	0.5	
	HCV and unknown diabetes	12	4.15	1.59	10.85	0.004	
HCV*donor age	No	3932	1	-	-	-	
	Yes	549	1.00	0.99	1.01	0.93	0.93
Recipient age*disease group	HCV	538	1.01	0.98	1.04	0.6	0.2
	ALD	1321	1	-	-	-	
	HBV	77	1.00	0.95	1.05	0.98	
	PSC	590	1.01	0.99	1.03	0.5	
	PBC	504	1.03	1.00	1.06	0.08	
	AID	387	1.00	0.98	1.02	0.9	
	Metabolic liver disease	383	1.00	0.97	1.02	0.8	
	Other liver disease	281	1.00	0.98	1.02	0.94	
	Retransplant	400	0.99	0.97	1.01	0.2	
Recipient age*ln(creatinine)		4481	1.02	1.01	1.03	0.004	0.004
Donor type *disease group	DBD or ALD	3970	0.74	0.44	1.24	0.3	0.6
	DCD and HCV	110	1	-	-	-	
	DCD and HBV	18	1.57	0.52	4.78	0.4	
	DCD and PSC	87	1.01	0.63	1.64	0.96	
	DCD and PBC	126	0.88	0.51	1.51	0.6	
	DCD and AID	57	0.63	0.31	1.27	0.2	
	DCD and Metabolic	72	1.35	0.77	2.35	0.3	
	DCD and other disease	35	0.88	0.40	1.91	0.7	
	DCD and retransplant	6	0.76	0.17	3.34	0.7	
Donor type*recipient age	DBD	3681	1	-	-	-	0.92
	DCD	800	1.00	0.98	1.02	0.92	
Donor type*ln(creatinine)	DBD	3681	1	-	-	-	0.0004
	DCD	800	0.44	0.28	0.69	0.0004	

Table A2 2C **Updated significant factors** **M2 results for non-cancer cohort**

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III p-values
Recipient							
Age at transplant		4481	0.94	0.89	0.99	0.03	-
Disease group	HCV	538	1.01	0.36	2.83	0.98	-
	ALD	1321	1	-	-	-	
	HBV	77	1.13	0.66	1.94	0.7	
	PSC	590	1.51	1.22	1.86	0.0002	
	PBC	504	0.96	0.75	1.22	0.7	
	AID	387	1.09	0.84	1.42	0.5	
	Metabolic	383	1.21	0.94	1.55	0.14	
	Other liver disease	281	1.31	0.98	1.76	0.07	
	Retransplant	400	1.70	1.27	2.27	0.0003	
HCV indicator	No	3932	1	-	-	-	-
	Yes	549	0.83	1.12	0.41	0.8	
Ln(creatinine)		4481	0.72	0.38	1.37	0.3	-
Renal replacement therapy	No	4238	1	-	-	-	0.07
	Yes	243	1.26	0.98	1.63	0.07	
Patient location	Outpatient	3570	1	-	-	-	0.03
	Inpatient	911	1.20	1.02	1.41	0.03	
Previous abdominal surgery	No	3621	1	-	-	-	0.04
	Yes	860	1.22	1.01	1.49	0.04	
Donor							
Donor age		4481	1.01	1.00	1.01	0.0002	0.0002
Donor cause of death	CVA	2903	1	-	-	-	0.06
	RTA	241	1.24	0.93	1.64	0.14	
	Other trauma	175	0.95	0.67	1.33	0.7	
	Other	1162	0.85	0.73	1.00	0.05	
History of diabetes	No	4119	1	-	-	-	-
	Yes	253	1.27	0.97	1.67	0.09	
	Unknown	109	0.82	0.51	1.32	0.4	
Donor type	DBD	3861	1	-	-	-	-
	DCD	800	51.58	7.89	337.32	<.0001	
Transplant							
Liver split	Whole	4087	1	-	-	-	0.05
	Split	394	1.30	1.01	1.69	0.05	
Interactions							
HCV*donor diabetes	No HCV; no diabetes	4440	1	-	-	-	0.017
	HCV and diabetes	29	1.26	0.65	2.83	0.4	
	HCV and unk diabetes	12	3.86	1.49	10.01	0.006	
Recipient age*ln(creatinine)		4481	1.02	1.00	1.03	0.02	0.02
Donor type*ln(creatinine)	DBD	3681	1	-	-	-	0.0004
	DCD	800	0.46	0.30	0.71	0.0004	

Table A2 3A **Currently applied M2 for cancer cohort**

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III p-values
Recipient							
Age at transplant		430	1.43	0.91	2.25	0.12	
Sex	Male	345	1	-	-	-	0.3
	Female	85	0.71	0.37	1.36	0.3	
HCV indicator	No	240	1	-	-	-	
	Yes	190	0.34	0.06	2.14	0.3	
Ln(creatinine)		430	127.10	0.36	45065.72	0.11	
Ln(bilirubin)		430	1.03	0.70	1.51	0.9	0.9
Ln(INR)		430	0.92	0.25	3.36	0.9	0.9
Sodium		430	1.05	0.99	1.11	0.09	0.09
Potassium		430	1.35	0.82	2.25	0.2	0.2
Albumin		430	1.02	0.98	1.06	0.3	0.3
Renal replacement therapy	No	413	1	-	-	-	0.2
	Yes	17	0.30	0.04	2.24	0.2	
Patient location	Outpatient	413	1	-	-	-	0.7
	Inpatient	17	0.80	0.22	2.89	0.7	
Previous abdominal surgery	No	383	1	-	-	-	0.9
	Yes	47	1.06	0.50	2.23	0.9	
Encephalopathy	No	389	1	-	-	-	0.2
	Yes	41	1.58	0.77	3.26	0.2	
Ascites	No	328	1	-	-	-	0.07
	Yes	102	1.69	0.97	2.94	0.07	
Ln(waiting time)		430	1.05	0.85	1.29	0.7	0.7
Diabetes	No	312	1	-	-	-	0.4
	Yes	118	1.27	0.74	2.20	0.4	
Ln(maximum AFP level)		430	1.05	0.93	1.20	0.4	0.4
Maximum tumour size		430	1.28	1.03	1.60	0.03	0.03
Number of tumours	1	283	1.00	-	-	-	0.7
	2	100	1.02	0.58	1.79	0.95	
	3 or more	47	0.70	0.30	1.65	0.4	
Donor							
Donor age		430	1.02	1.00	1.04	0.09	
Donor cause of death	CVA	285	1	-	-	-	0.3
	RTA	14	2.31	0.73	7.25	0.15	
	Other trauma	17	0.42	0.10	1.85	0.3	
	Other	114	1.00	0.59	1.69	0.99	

Donor BMI		430	0.98	0.94	1.04	0.5	0.5
History of diabetes	No	392	1	-	-	-	
	Yes	23	1.18	0.27	5.15	0.8	
	Unknown	15	0.94	0.12	7.29	0.95	
Donor type	DBD	311	1	-	-	-	
	DCD	119	5.74	0.001	29899.16	0.7	
Blood group compatibility	Identical	422	1	-	-	-	0.03
	Compatible	8	3.54	1.13	11.11	0.03	
Liver split	Whole	396	1	-	-	-	0.4
	Reduced	34	1.53	0.54	4.35	0.4	
Interactions							
HCV*donor diabetes	HCV=No or donor diabetes=No	416	1	-	-	-	0.2
	HCV and diabetes	9	4.50	0.78	25.96	0.09	
	HCV; unk diabetes	5	2.58	0.14	47.27	0.5	
HCV*donor age	No	240	1	-	-	-	0.10
	Yes	190	1.03	0.99	1.06	0.10	
Recipient age*ln(creatinine)		430	0.92	0.83	1.02	0.11	0.11
Donor type*recipient age	DBD	311	1.00	-	-	-	0.3
	DCD	119	1.04	0.97	1.11	0.3	
Donor type*ln(creatinine)	DBD	311	1.00	-	-	-	0.4
	DCD	119	0.48	0.08	2.77	0.4	

Table A2 3B **Updated FULL M2 cancer results**

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III p-values
Recipient							
Age at transplant		1033	0.98	0.77	1.25	0.9	-
Sex	Male	831	1	-	-	-	0.5
	Female	202	0.90	0.65	1.24	0.5	
HCV indicator	No	565	1	-	-	-	-
	Yes	468	0.78	0.34	1.81	0.6	
Ln(creatinine)		1033	0.86	0.03	22.40	0.93	-
Ln(bilirubin)		1033	1.11	0.91	1.35	0.3	0.3
Ln(INR)		1033	0.67	0.35	1.29	0.2	0.2
Sodium		1033	1.01	0.98	1.04	0.7	0.7
Potassium		1033	1.06	0.82	1.37	0.7	0.7
Albumin		1033	1.01	0.99	1.03	0.2	0.2
Renal replacement therapy	No	987	1	-	-	-	0.7
	Yes	46	0.87	0.48	1.60	0.7	
Patient location	Outpatient	994	1	-	-	-	0.16
	Inpatient	39	1.55	0.84	2.87	0.16	
Previous abdominal surgery	No	927	1	-	-	-	0.2
	Yes	106	1.26	0.86	1.84	0.2	
Encephalopathy	No	904	1	-	-	-	0.4
	Yes	129	0.85	0.57	1.25	0.4	
Ascites	No	758	1	-	-	-	0.03
	Yes	275	1.37	1.03	1.83	0.03	
Ln(waiting time)		1033	1.07	0.96	1.19	0.2	0.2
Diabetes	No	717	1	-	-	-	0.5
	Yes	316	1.11	0.84	1.45	0.5	
Ln(maximum AFP level)		1033	1.05	0.97	1.13	0.2	0.2
Maximum tumour size		1033	1.12	0.99	1.26	0.07	0.07
Number of tumours	1	686	1	-	-	-	0.97
	2	229	0.97	0.72	1.33	0.9	
	3 or more	118	0.96	0.65	1.41	0.8	
Donor							
Donor age		1033	1.01	1.00	1.02	0.12	0.006
Donor cause of death	CVA	647	1	-	-	-	0.8
	RTA	48	0.96	0.52	1.79	0.91	
	Other trauma	36	0.98	0.49	1.94	0.95	
	Other	302	1.12	0.86	1.47	0.4	
Donor BMI		1033	1.00	0.97	1.02	0.7	0.7

History of diabetes	No	919	1	-	-	-	-
	Yes	81	1.99	1.21	3.27	0.007	
	Unknown	33	1.94	0.99	3.81	0.05	
Donor type	DBD	678	1	-	-	-	-
	DCD	355	43.77	0.73	2619.56	0.07	
Blood group compatibility	Identical	1016	1	-	-	-	0.07
	Compatible	17	1.93	0.94	3.98	0.07	
Liver split	Whole	976	1	-	-	-	0.009
	Reduced	57	2.05	1.20	3.50	0.009	
Interactions							
HCV*donor diabetes	HCV=No or donor diabetes=No	991	1	-	-	-	0.9
	HCV and diabetes	33	0.92	0.42	2.02	0.8	
	HCV; unk diabetes	9	0.72	0.18	2.79	0.6	
HCV*donor age	No	565	1	-	-	-	0.3
	Yes	468	1.01	0.99	1.02	0.3	
Recipient age*ln(creatinine)		1033	1.01	0.95	1.06	0.8	0.8
Donor type*recipient age	DBD	678	1	-	-	-	0.5
	DCD	355	0.99	0.95	1.02	0.5	
Donor type*ln(creatinine)	DBD	678	1	-	-	-	0.18
	DCD	355	0.56	0.24	1.32	0.18	

Table A2 3C **Updated Statistically significant M2 cancer results**

Term	Level	N	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald test p-values	Type III p-values
Recipient							
Albumin	Linear	1033	1.02	1.00	1.03	0.03	0.04
Ascites	No	758	1	-	-	-	0.03
	Yes	275	1.33	1.03	1.72	0.03	
Max tumour size	Linear	1033	1.10	0.99	1.23	0.08	0.08
Donor							
Donor age	Linear	1033	1.01	1.00	1.02	0.005	0.005
History of diabetes	No	919	1	-	-	-	0.001
	Yes	81	1.87	1.28	2.72	0.001	
	Unknown	33	1.76	1.00	3.09	0.05	
Donor type	DBD	678	1	-	-	-	0.0001
	DCD	355	1.63	1.27	2.09	0.0001	
Blood group compatibility	Identical	1016	1	-	-	-	0.07
	Compatible	17	1.95	0.96	3.97	0.07	
Liver split	Whole	976	1	-	-	-	0.02
	Reduced	57	1.91	1.13	3.22	0.02	

Table A2 4 **C-statistics (95% CI) for current and updated M2 models**

	Non-cancer	Cancer
Current	0.62 (0.59, 0.64)	0.70 (0.64, 0.75)
Updated full	0.61 (0.59, 0.63)	0.61 (0.59, 0.65)
Updated significant	0.60 (0.59, 0.62)	0.60 (0.57, 0.63)

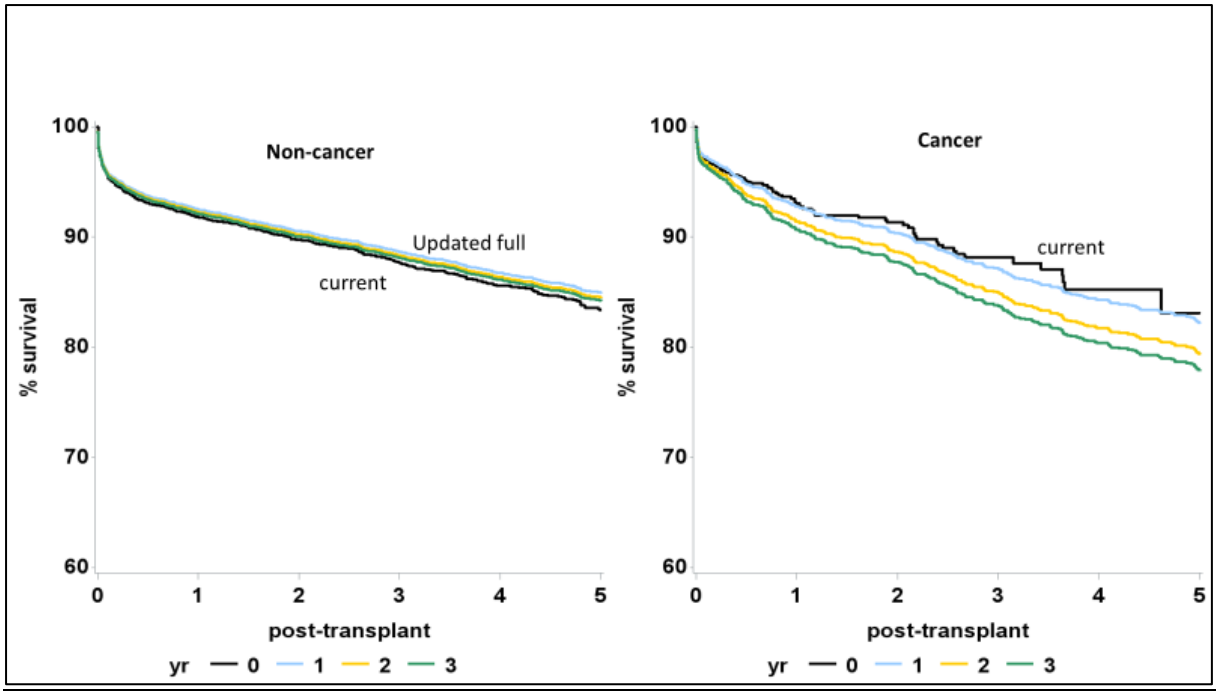

Figure A2 1 Risk-adjusted survival for an average transplant in the current and updated cohorts.

Appendix 3

7. Simulation cohort and description

7.1. All UK adult elective NHS group 1 registrations for a liver only transplant who were active on the list between 1 April 2018 and 31 March 2019 were extracted from the UK Transplant Registry as at 27 October 2020. These registrations included patients either already active on 1 April 2018 or new registrations with an 'active' status during 1 April 2018 and 31 March 2019.

7.2. The following registrations were excluded from the registration cohort:

- 7.2.1. Registrations resulting in a living or domino donor liver transplant
- 7.2.2. Regraft registrations for patients who received more than one transplant during 2018. This, so that patient lifetime is not double counted
- 7.2.3. Registrations resulting in a multi-organ transplant
- 7.2.4. Registrations resulting in a reduced liver transplant
- 7.2.5. Registrations resulting in a heterotopic transplant (n=1)
- 7.2.6. Registrations that ended in a transplant on the 1st April 2018 but Organ and Tissue Donation and Transplantation (OTDT) were notified of the donor prior to 1st April 2018.
- 7.2.7. Two adults receiving a split liver from the same donor during 2018/2019
- 7.2.8. Retrospective registrations
- 7.2.9. Patients who were only ever suspended (n=2)
- 7.2.10. Registrations with missing renal replacement therapy or patient location information at time of registration
- 7.2.11. Registrations for patients with cancer but no cancer information recorded
- 7.2.12. Variant syndrome patients regardless of UKELD
- 7.2.13. Paediatric patients not dual-listed

7.3. The complete case cohort was 1194 registrations and 559 DBD donors whose liver was transplanted into either an adult or large paediatric elective CLD or HCC patient as either a whole or a split liver during 2018/2019.

7.4. DCD donors were excluded from the cohort as they are currently offered on a centre basis. However, patients who ultimately received a liver from a DCD donor were included in the registration cohort.

7.5. The donor notification date and time to the ODT Hub office was used to determine the order each donor appears in the simulation. The registration pool for each donor were all registrations that were active on the liver only transplant list at the time of notification. The latest sequential information on clinical variables (creatinine, bilirubin, sodium, INR, albumin, potassium, renal replacement therapy and patient location) prior to the notification date was then added and the registration pool was then further restricted to registrations that were blood group compatible and weight compatible (latest recipient weight ±20kg of the donor weight). A restriction was imposed so that blood group O donors were preferentially allocated to O recipients first and subsequently to all other compatible recipients. This is in agreement with the current allocation policy.

7.6. At each point in time when a donor occurred, the registration dataset was then split into non-cancer and cancer datasets based on the disease at registration. For both datasets, separately, the expected survival post-registration (M1) and post-transplant (M2) was calculated. The cancer and non-cancer datasets were then combined and livers were allocated based on the TBS score.:

7.7. Patients who were transplanted in real-life but not transplanted under a model, presented the problem of not having an observed death date on the list. Therefore, we estimated a death date on the list for these patients using M1 from the date on which the real-life transplant was performed. These patients were kept on the pool of potential recipients in the model simulations until either an organ was allocated to them or their estimated date of death was reached. Registrations who were allocated an organ were excluded from the pool of patients for the simulation where they were allocated.

8. Deaths on the list or removals from the list due to condition deteriorated
   8.1. The number of patients who died or were removed due to condition deteriorated includes the number of patients who died or were removed in real life during 2018/2019 without being allocated a liver in the simulations. It also includes patients who were transplanted in real-life but not under a model and whose estimated death date on the list using M1 was during 2018/2019. This is one of the primary outcomes of the simulation.

9. Patient life years
   9.1. Patient life years was calculated for all registrations in the cohort and depended upon the registration outcome.
      9.1.1. *Patients allocated a liver*: observed survival time from registration to date of notification of a liver offer plus the expected survival post-transplant using M2
      9.1.2. *Patients removed (regardless of reason for removal from the list), died or suspended during 2018/2019*: observed survival time from registration to removal date, death date or date of suspension.
      9.1.3. *Patients active on 1 April 2019*: observed survival time from registration to 1 April 2019 plus expected survival post-registration from end of simulation period using M1

   9.2. The following M1 models were used to calculate 9.1
      9.2.1.1. Observed updated models with earliest baseline year group (2006-2008 for non-cancer and 2009-2012 for cancer) (S9)
      9.2.1.2. Observed parameter estimates from the updated models with earliest baseline year group (2006-2008 for non-cancer and 2009-2012 for cancer) and the simulated M1 baseline survival functions for both cancer and non-cancer (S11)
      9.2.1.3. Observed parameter estimates from the updated models with latest baseline year group (2013-2016 for both) and the simulated M1 baseline survival functions for both cancer and non-cancer (S12)

   9.3. The observed survival time includes periods of suspension. Total patient years were then summed up across all registrations

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