

NHS BLOOD AND TRANSPLANT

LIVER ADVISORY GROUP

LIVER SPLITTING ACTIVITY REPORT

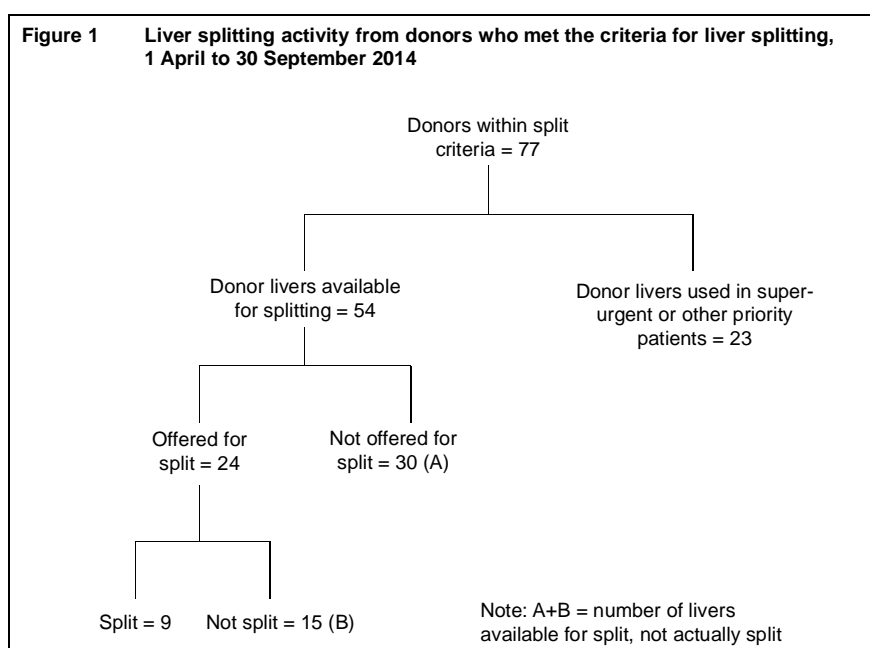
SUMMARY

BACKGROUND

- 1 Donors after brain death (DBD) aged < 40 years, weighing > 50kg and known to have spent < five days in intensive care meet the criteria for liver splitting. If a donated liver is split it can be used to transplant two patients; typically one adult and one paediatric. This paper reports on the outcome of livers from DBD who donated their liver in a recent time period and who met the criteria for liver splitting. It also reports on survival outcomes of patients who received split liver transplants.

DATA ANALYSIS

- 2 **Figure 1** shows a summary of the liver splitting activity in the period 1 April to 30 September 2014. In just over half of the 30 cases where the liver was available for splitting but was not offered for splitting, abnormal or raised liver function tests were cited as the reason for not considering splitting. Fifteen livers were offered for splitting but instead used whole or reduced; common reasons were the fattiness of the organ or a lack of suitable patients for the left lateral segment.



- 3 Analyses of transplant survival following split liver transplantation in paediatric and adult patients showed no evidence of an impact on transplant survival up to five years depending on whether the split liver was retained or imported for paediatric patients, but for adult patients there was some evidence of superior survival for retained split livers (Log-rank test: $p=0.03$). There was no difference found between the survival of livers split by adult unit surgeons and livers split by paediatric unit surgeons.

LAG IS ASKED TO NOTE

- 4 The completion of the Split Liver Information form is the most reliable way of recording data on where liver splitting is performed and by whom on the UK Transplant Registry to inform analyses (currently the return rate is approximately 90%).

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October 2014

NHS BLOOD AND TRANSPLANT

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LIVER SPLITTING ACTIVITY REPORT

INTRODUCTION

- 1 If a liver from a deceased donor is split it can be used to transplant two patients; typically an adult patient receives the right liver lobe and a paediatric patient receives the left lobe or the left lateral segment. This paper reports on the outcome of livers from donors after brain death (DBD) who donated their liver between 1 April and 30 September 2014 and who met the criteria for liver splitting.
- 2 The paper also reports on a comparison of survival outcomes for patients who received a split liver transplant using livers from DBD donors, between 1 April 2006 and 31 March 2014, where the split liver was retained by the centre where the splitting was performed versus those where the split liver was imported from another centre. A comparative analysis was also performed between split livers that were split by adult unit surgeons versus those that were split by paediatric unit surgeons. Finally, a comparison of the unadjusted survival of whole versus split livers transplanted into adult patients is also shown.

LIVER SPLITTING ACTIVITY

Data and methods

- 3 Data were obtained from the UK Transplant Registry (UKTR) on the 77 UK DBD donors whose liver was donated between 1 April and 30 September 2014 and who met the criteria for liver splitting. These were donors under 40 years of age, weighing more than 50kg and were known to have spent less than five days in an intensive care unit (ICU). The time in ICU was calculated as the time lapse between start of ventilation and time of second test for brainstem death. These livers were transplanted in the UK or the Republic of Ireland.
- 4 For comparison, data were also obtained on the 75 UK DBD whose liver was donated between 1 October 2013 and 31 March 2014 and who met the criteria for liver splitting. These livers were also transplanted in the UK or the Republic of Ireland.
- 5 Donated livers were classed as split livers when they were used to transplant two patients and as reduced livers when cut down and used for one patient. Consequently reduced livers were not classed as split livers.
- 6 Livers were classed as offered for splitting if there was a record in the UKTR stating that part of the liver had been offered to a centre (offers that were withdrawn were discounted), as recorded by the ODT Duty Office.

Results

- 7 The status of each liver that was transplanted is shown in **Table 1** for April to September 2014, with October 2013 to March 2014 figures for comparison. Between 1 April and 30 September 2014, of the 77 DBD donors meeting the splitting criteria (75 between 1 October 2013 and 31 March 2014), 54 (70%) livers were available for splitting (52 (69%) between October 2013 and March 2014). Of these 54 livers, 24 (44%) were offered for splitting (24 of the 52 (46%) between October 2013 and March 2014). Of the 24 livers offered for splitting, 9 (38%) were actually split (13 (54%) were split between October 2013 and March 2014). This activity is summarised in **Figure 1**.

Table 1 Donors meeting criteria for liver splitting, by donor allocation zone, 1 April to 30 September 2014 (1 October 2013 to 31 March 2014)

Donor allocation zone	Total meeting liver splitting criteria and transplanted N		Super-urgent liver or intestinal/ hepatoblastoma recipients N _{P1}		Elective intestinal/ multi-organ recipients N _{P2}		Available for splitting N _A		Offered for splitting				Split				Whole N _w		Reduced N _r	
Birmingham	20	(13)	5	(4)	0	(1)	15	(8)	6	(2)	40	(25)	3	(1)	50	(50)	3	(1)	0	(0)
Cambridge	10	(6)	3	(4)	0	(0)	7	(2)	1	(1)	14	(50)	0	(0)	0	(0)	1	(1)	0	(0)
Edinburgh	11	(9)	2	(2)	0	(2)	9	(5)	5	(5)	56	(100)	3	(1)	60	(20)	2	(3)	0	(1)
King's College	11	(17)	5	(2)	1	(1)	5	(14)	1	(5)	20	(36)	1	(4)	100	(80)	0	(1)	0	(0)
Leeds	9	(16)	3	(2)	0	(0)	6	(14)	3	(7)	50	(50)	1	(5)	33	(71)	2	(2)	0	(0)
Newcastle	7	(6)	1	(2)	1	(0)	5	(4)	4	(3)	80	(75)	1	(1)	25	(33)	3	(2)	0	(0)
Royal Free	9	(8)	1	(3)	1	(0)	7	(5)	4	(1)	57	(20)	0	(1)	0	(100)	4	(0)	0	(0)
TOTAL	77	(75)	20¹	(19²)	3³	(4⁴)	54	(52)	24	(24)	44	(46)	9	(13)	38	(54)	15	(10)	0	(1)

¹ Seven of these livers were split and used to transplant one super-urgent/ hepatoblastoma recipient and one elective liver only recipient

² Three of these livers were split and used to transplant one super-urgent/ hepatoblastoma recipient and one elective liver only recipient

³ None of these livers were split

⁴ Two of these livers were split and used to transplant one multi-organ/ elective intestinal recipient and one elective liver only recipient

Note: Due to small numbers the percentages presented must be viewed with caution

Livers were not necessarily transplanted by the centre that resides in the donor allocation zone

$N = N_{P1} + N_{P2} + N_A$; $N_o = N_s + N_w + N_r$

- 8 These 77 livers resulted in 93 transplants, of which 19 (20%) were performed in paediatric patients (the 75 livers between October 2013 and March 2014 resulted in 93 transplants too, 19 (20%) of which were performed in paediatric patients).
- 9 **Table 2** details the reasons given by the transplanting centre or noted by the ODT Duty Office for 30 livers not being offered for splitting (67% of the 45 livers available for splitting that were not split). In 17 cases there were concerns over liver function tests. The donor AST level, reported on the Core Donor Data Form, is presented in the table but it was only reported for 50% of donors.

Table 2 Reasons given for why 30 livers from donors meeting the liver splitting criteria, between 1 April and 30 September 2014, were not offered for splitting

Donor	Donor allocation zone	Transplanting centre	Reason for liver not being offered for splitting	AST (iu/l)
Donor reasons				
1	Birmingham	Birmingham	Co-morbidities and past medical history	.
2	Birmingham	Birmingham	Raised liver function tests (Alanine transaminase ALT 354 iu/l)	.
3	Birmingham	Birmingham	Liver function tests and medical History	.
4	Birmingham	Birmingham	Transaminases raised	.
5	Birmingham	Birmingham	Raised liver function tests	.
6	Birmingham	Birmingham	Raised liver function tests and history of excess alcohol	.
7	Cambridge	Cambridge	Raised liver function tests (Alanine transaminase ALT 424 iu/l)	.
8	Cambridge	Newcastle	Function and donor unstable	.
9	Edinburgh	Edinburgh	Abnormal liver function tests	318
10	Edinburgh	Edinburgh	Liver function tests and laceration to right lobe	309
11	Edinburgh	Edinburgh	Raised liver function tests (Alanine transaminase ALT 280 iu/l)	538
12	Edinburgh	Royal Free	Donor history, liver function tests and mildly/moderately fatty liver	39
13	King's College	King's College	Moderately fatty	.
14	King's College	King's College	Fatty liver	.
15	King's College	King's College	Raised liver function tests (Alanine transaminase ALT 277 iu/l)	.
16	King's College	King's College	Fatty liver and past medical history (documents didn't record what history was problematic)	.
17	Leeds	Leeds	Abnormal liver function tests	.
18	Leeds	Leeds	Function - (Alanine transaminase ALT 660 iu/l)	337
19	Leeds	Leeds	Fatty liver	.
20	Newcastle	Leeds	Raised liver function tests (Alanine transaminase ALT 1688/1727/2168 iu/l - multiple readings)	.
21	Royal Free	Royal Free	Abnormal liver function tests	241
22	Royal Free	Royal Free	Raised liver function tests (Alanine transaminase ALT 238 iu/l)	266
23	Royal Free	Royal Free	Raised liver function tests	.
Recipient reasons				
24	Cambridge	Leeds	All other paediatric centres declined due to no suitable recipients	.
25	Cambridge	Newcastle	Large recipient, needed a whole liver	.
Other reasons				
26	Birmingham	Birmingham	Recipient was large and liver was already going to be marginally too small for him, even without splitting	.
27	Birmingham	Birmingham	Not splittable as being put onto Organ OX machine as part of the COPE 2 trial	.
28	Birmingham	Edinburgh	Edinburgh say Birmingham made decision on splitting. Birmingham say they offered on and they didn't make decision not to split (weight 160kg)	.

Table 2 Reasons given for why 30 livers from donors meeting the liver splitting criteria, between 1 April and 30 September 2014, were not offered for splitting

Donor	Donor allocation zone	Transplanting centre	Reason for liver not being offered for splitting	AST (iu/l)
29	Cambridge	Birmingham	Warm Ischaemic Time	
30	Cambridge	Edinburgh	Duty Office informed centre the liver was unsuitable for splitting due to ITU stay (incorrectly)	

- 10 The reasons given for not splitting the remaining 15 livers that were offered for splitting but were not split (33% of the 45 livers available for splitting that were not split) are detailed in **Table 3**.

Table 3 Reasons given for why 15 livers from donors meeting the split liver criteria, between 1 April and 30 September 2014, that were offered for splitting were not split

Donor	Donor allocation zone	Transplanting centre	Details of why liver was not split
Donor reasons			
1	Birmingham	Birmingham	Up to date blood gases and patient history
2	Birmingham	Birmingham	Anatomy - biliary drainage unsuitable
3	Cambridge	Cambridge	Offered and left lateral segment accepted by Birmingham, then declined as fatty
4	Edinburgh	Edinburgh	Left lateral segment declined by all centres on function
5	Leeds	Edinburgh	Moderately fatty
6	Leeds	Leeds	Moderately steatotic
7	Newcastle	Leeds	Left lateral segment offered and declined by all centres on virology
8	Royal Free	Leeds	Left lateral segment offered and then offer withdrawn due to size and anatomy
9	Royal Free	Royal Free	Left lateral segment accepted by King's but deemed untransplantable so whole liver went to Royal Free
10	Royal Free	Royal Free	Birmingham said left lobe was too big, King's said it was a little fatty. Liver had a sub capsular haematoma old on the caudate
Other reasons			
11	Birmingham	Birmingham	Left lateral segment offered and declined by all centres as no suitable recipients
12	Edinburgh	Newcastle	Left lateral segment offered and declined by all centres on history and no suitable recipients
13	Newcastle	Edinburgh	Left lateral segment declined by all centres on size and no suitable recipients (ABO)
14	Newcastle	Newcastle	Declined on distance/centre busy/no suitable recipients
15	Royal Free	Royal Free	Anatomy and 1.1kg liver (right lobe would have been too small for Royal Free recipient)

TRANSPLANT SURVIVAL

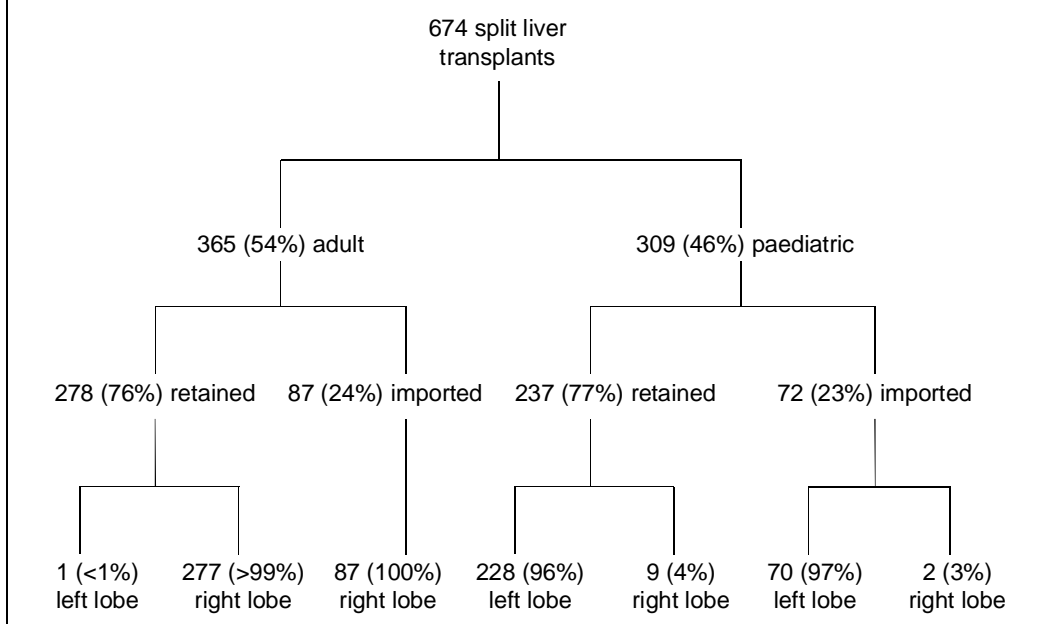
Data and methods

- 11 Data on 674 NHS group 1 first elective split liver only transplants in the UK using livers from DBD donors between 1 April 2006 and 31 March 2014 were analysed. Heterotopic, auxiliary and intestinal transplants were excluded from this cohort as were regrafts. Follow-up data were as recorded on the UKTR on 20 October 2014.
- 12 Each split liver was categorised into “retained”/ “imported” and “split by adult unit surgeon”/ “split by paediatric unit surgeon” (where surgeons from Birmingham, King’s College and Leeds are classed as paediatric unit surgeons). Data returned via the Split Liver Information form was the primary source for categorising split livers into these groups. “Retained”/ “imported” was determined using the centre where the splitting was performed, which was reported in 55% of cases, and “split by adult unit surgeon”/ “split by paediatric unit surgeon” was determined by the centre where the splitting surgeon was appointed, which was reported in 57% of cases. The secondary source for finding out this information was the ODT Duty Office notes. If it was not clear from these notes where the liver was split and who performed the split, a judgement call was made (for instance, if the zonal centre was a paediatric centre who retained the left lobe and exported the right lobe, then we assumed that the paediatric centre performed the split in-house if the primary and secondary sources were insufficient).
- 13 Survival up to five years post-split liver transplant was compared for “retained” and “imported” split livers and for “adult unit surgeon” and “paed unit surgeon” split livers, separately for adult and paediatric patients. These analyses were performed using the Kaplan-Meier estimation method and the log-rank test. There was no risk-adjustment made to control for confounding factors. Median cold ischaemic time (CIT) was also compared, for retained and imported split livers, using the Mann-Whitney U test.
- 14 A comparison of the survival of whole and split liver transplants up to five years was also made, for adult recipients only. This analysis included 3,184 NHS group 1 first adult elective patients transplanted in the UK between 1 April 2006 and 31 March 2014. A sub-group analysis was performed on just those transplants performed between 1 April 2010 and 31 March 2014 (N=1,706). Again, heterotopic, auxiliary and multi-organ transplants and regrafts were excluded and follow-up data were as recorded on the UKTR on 20 October 2014.

Results

- 15 **Figure 2** shows a breakdown of the 674 split liver transplants by recipient age group (adult (≥ 17 years), paediatric (< 17 years)) and whether the liver was retained or imported.

Figure 2 Breakdown of NHS group 1 elective split liver only transplants in the UK using livers from donors after brain death, 1 April 2006 to 31 March 2014



16 **Table 4** shows a breakdown of the 674 split liver transplants by recipient age group, transplant centres and whether the liver was retained or imported.

Table 4 NHS group 1 first elective split liver only transplants in the UK using livers from donors after brain death, 1 April 2006 – 31 March 2014

Transplant centre	Retained N	Imported N	Total
Paediatric recipients			
Birmingham	91	19	110
King's College	107	40	147
Leeds	39	13	52
Total	237	72	309
Adult recipients			
Birmingham	112	3	115
Cambridge	13	12	25
Edinburgh	21	38	59
King's College	83	3	86
Leeds	36	7	43
Newcastle	4	8	12
Royal Free	9	16	25
Total	278	87	365
TOTAL	515	159	674

- 17 **Table 5** shows the median and range of CIT, in hours, of retained and imported split livers transplanted in adult and paediatric patients (left lobes transplanted in adult patients and right lobes transplanted in paediatric patients were excluded (N=12)). On average, CIT was 2.7 hours longer for imported liver lobes compared with retained liver lobes for both adult and paediatric recipients (Mann-Whitney U test: $p < 0.0001$ for both).

Table 5 Cold ischaemic times (CIT) of retained and imported split livers, transplanted in NHS group 1 elective liver only patients in the UK between 1 April 2006 and 31 March 2014			
	N ¹	CIT (hours)	
		Median	Range
Left lobes transplanted in paediatric patients			
Retained	185	9.0	3.6 – 16.2
Imported	57	11.7	2.9 – 16.5
Right lobes transplanted in adult patients			
Retained	261	9.7	3.9 – 17.6
Imported	84	12.4	6.6 – 16.3

¹ CIT was not reported for a total of 75 split livers

Unadjusted survival analysis

- 18 **Figure 3** shows the Kaplan-Meier estimated survival curves up to five years post-transplant (where the outcome event is graft failure or patient death) for paediatric and adult patients, by whether the split liver was retained or imported. The estimated five year transplant survival rates for paediatric patients were very similar for retained and imported split livers, at approximately 82%. The log-rank test showed no statistical difference in the overall survival curves in the paediatric analysis ($p=0.9$). Contrastingly, there was a significant difference between the survival curves in the adult analysis ($p=0.03$). The estimated five year transplant survival rates for imported and retained livers were approximately 68% and 80% but there was some overlap in confidence intervals (53%-78% and 74%-85%, respectively).
- 19 **Figure 4** shows the Kaplan-Meier estimated survival curves up to five years post-transplant (where the outcome event is graft failure or patient death) for paediatric and adult patients, by whether the liver was split by an adult unit surgeon or a paediatric unit surgeon. Note that there were only six events in the “split by adult unit surgeon” group in the paediatric analysis and only eight in the adult analysis, so the results should be viewed with caution. There was no statistically significant difference found between these groups in the paediatric or adult analysis. The estimated five year transplant survival rates for livers split by adult unit surgeons and livers split by paediatric unit surgeons were approximately 80% (56%-91%) and 83% (77%-87%), respectively, for paediatric patients and 80% (63%-90%) and 77% (71%-82%), respectively, for adult patients.
- 20 Causes of graft failure or patient death that were reported to the UKTR for the 117 out of 674 split liver transplant recipients who died or whose graft failed within five years following transplant are presented for reference in **Appendix I** by age group, by whether the split liver was retained/ imported and by whether the liver was split by an adult/ paediatric unit surgeon.

Figure 3 Comparison of five year transplant survival of retained and imported split livers transplanted in NHS group 1 elective patients in the UK between 1 April 2006 and 31 March 2014

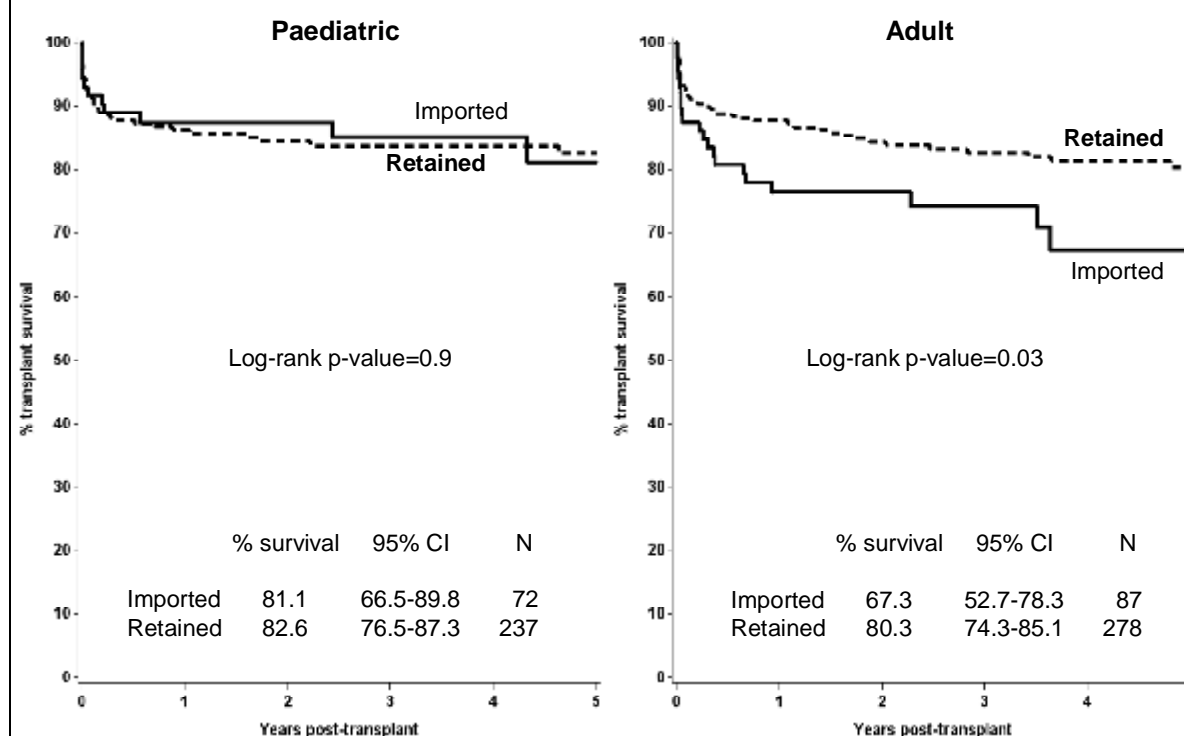
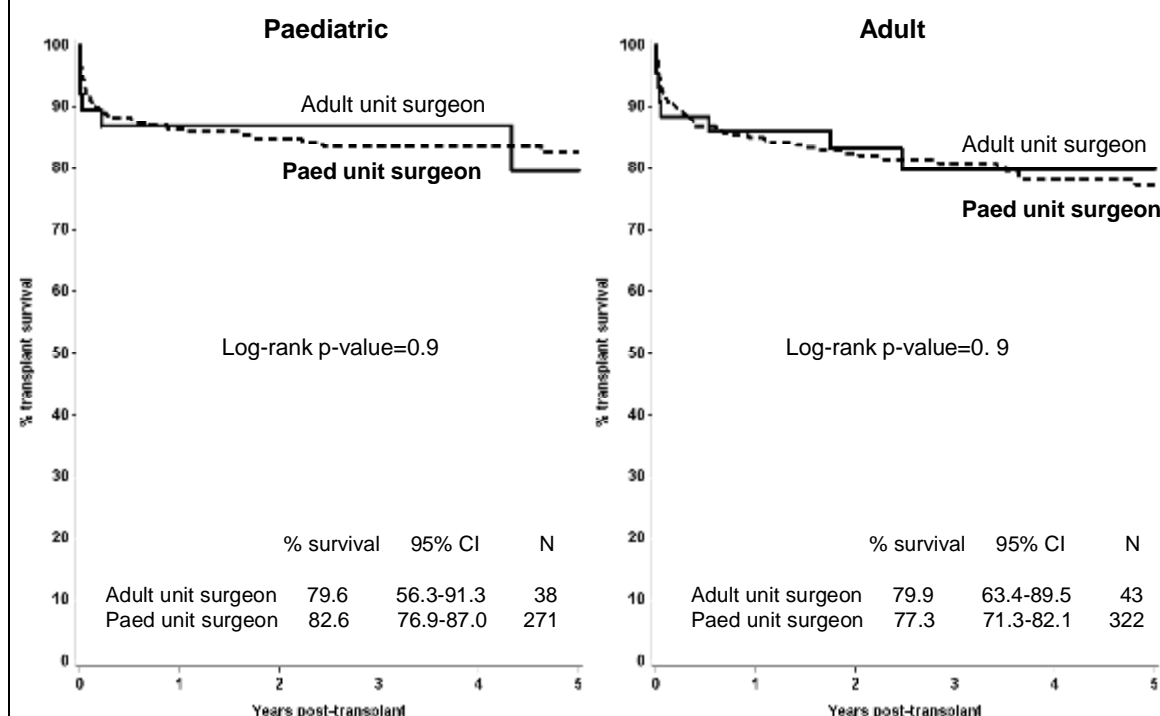
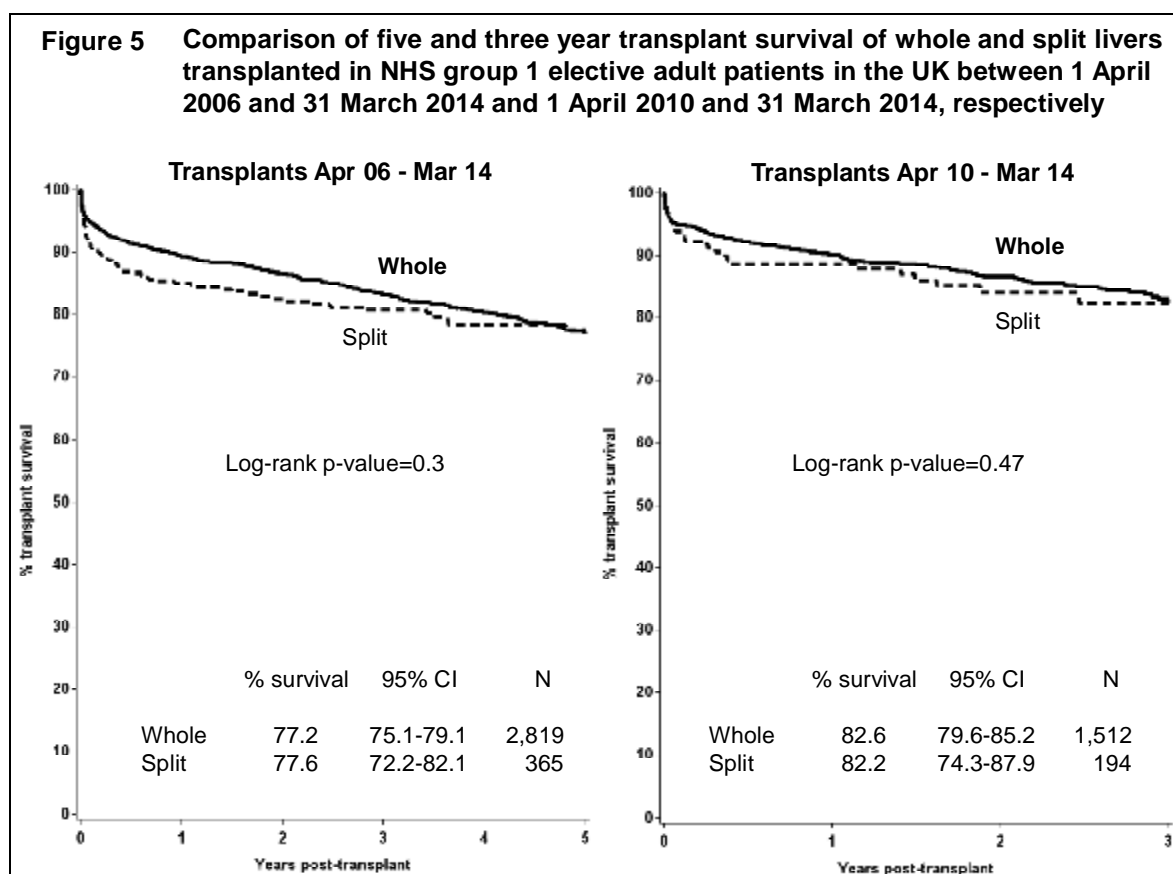


Figure 4 Comparison of five year transplant survival of livers split by adult and paediatric unit surgeons, transplanted in NHS group 1 elective patients in the UK between 1 April 2006 and 31 March 2014



21 **Figure 5** shows the Kaplan-Meier estimated survival curves comparing transplant survival (where the outcome event is graft failure or patient death) up to five years for

whole and split liver transplants between 1 April 2006 and 31 March 2014 and up to three years for whole and split liver transplants in the reduced cohort of 1 April 2010 to 31 March 2014. For transplants between April 2006 and March 2014, the unadjusted analysis suggests that the long-term survival of whole and split liver transplants is similar; however shorter-term (<2 years) survival appears to be superior for whole liver transplants. For just those transplants carried out more recently, between April 2010 and March 2014, there is no difference in the unadjusted survival curves up to three years ($p=0.47$).



- 22 Data on 35 NHS group 1 first super urgent split liver only transplants in the UK using livers from DBD donors between 1 April 2006 and 31 March 2014 were also analysed. Heterotopic, auxiliary and intestinal transplants were excluded from this cohort as were regrafts. Follow-up data were as recorded on the UKTR on 22 October 2014. Of these there were 9 (30%) deaths or failed grafts in the 30 adult recipients, and 2 (40%) deaths or failed grafts in the 5 paediatric recipient. Due to these small numbers no survival analysis could be performed.

SUMMARY

- 23 There were 77 livers donated between 1 April 2014 and 30 September 2014 from donors who met the criteria for liver splitting (3% more than previous six months, Oct 2013-Mar 2014). Of these, 54 (70%) were available for splitting for elective recipients, having not been used in super-urgent, hepatoblastoma, intestinal or multi-organ recipients. Of these, 24 (44%) were offered for splitting and 9 (38% of the 24) were actually split (31% fewer than previous six months, Oct 2013-Mar 2014). In just over half of the 30 cases where the liver was available for splitting but was not offered for splitting, abnormal or raised liver function tests were cited as the reason for not considering splitting. Fifteen livers were offered for splitting but instead used whole or reduced. Common reasons for not splitting these livers were the fattiness of the organ or a lack of suitable patients for the left lateral segment.
- 24 An unadjusted analysis of survival following split liver transplantation, comparing retained and imported split livers transplanted between 1 April 2006 and 31 March 2014, showed no evidence of an impact on transplant survival up to five years depending on whether the split liver was retained or imported for paediatric patients, but for adult patients there was some evidence of superior survival for retained split livers (Log-rank test: $p=0.03$). An unadjusted survival analysis on the same cohort comparing livers that were split by adult unit surgeons and livers that were split by paediatric unit surgeons showed no difference in transplant survival up to five years for paediatric or adult patients.
- 25 A comparison of unadjusted survival estimates following whole and split liver transplantation in adult patients, between 1 April 2006 and 31 March 2014, showed that the long-term survival of whole and split liver transplants is similar; however shorter-term (<2 years) survival appears to be superior for whole liver transplants.

LAG IS ASKED TO NOTE

- 26 The completion of the Split Liver Information form is the most reliable way of recording data on where liver splitting is performed and by whom on the UKTR to inform analyses (currently the return rate is approximately 90%).

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October 2014

Appendix I

Causes of graft failure or patient death for NHS group 1 elective split liver only transplant recipients in the UK between 1 April 2006 and 31 March 2014 who died or whose graft failed within five years following transplant, by age group, whether the split liver was retained/imported and whether the liver was split by an adult/ paediatric unit surgeon

Causes of graft failure or patient death	Retained split liver N	Imported split liver N	Liver split by paediatric unit surgeon N	Liver split by adult unit surgeon N	Total N
PAEDIATRIC PATIENTS					
<i>Cause of graft failure - patient did not die</i>					
Hepatic artery thrombosis	11	3	12	2	14
Primary non-function	3	2	3	2	5
Chronic rejection	1	1	2	0	2
Other	4	0	4	0	4
Not reported	1	0	1	0	1
Total	20	6	22	4	26
<i>Cause of death</i>					
Multi-system failure	3	2	5	0	5
Septicaemia	2	1	3	0	3
Primary non-function -> multi-system failure	2	0	2	0	2
Recurrent disease	3	0	3	0	3
Other	6	1	6	1	7
Not reported	1	1	1	1	2
Total	17	5	20	2	22
TOTAL (% of total splits)	37 (16)	11 (15)	42 (15)	6 (16)	48 (15)
ADULT PATIENTS					
<i>Cause of graft failure - patient did not die</i>					
Hepatic artery thrombosis	13	5	15	3	18
Other	4	3	6	1	7
Total	17	8	21	4	25
<i>Cause of death</i>					
Multi-organ failure	5	4	8	1	9
Hepatic artery thrombosis -> multi-system failure/myocardial infarction/pulmonary infection	3	2	4	1	5
Non-lymphoid malignant disease	4	0	4	0	4
Recurrent disease	2	3	5	0	5
Non-thrombotic infarction -> multi-system failure/septicaemia	2	0	2	0	2
Cerebro-vascular accident	2	0	2	0	2
Renal failure	2	0	2	0	2
Vascular occlusion -> multi-system failure	2	0	2	0	2
Rejection/primary non-function	1	1	1	1	2
Other	5	3	7	1	8
Not reported	2	1	3	0	3
Total	30	14	40	4	44
TOTAL (% of total splits)	47 (17)	22 (25)	61 (19)	8 (19)	69 (19)