NHS BLOOD AND TRANSPLANT

LIVER ADVISORY GROUP

LIVER SPLITTING ACTIVITY REPORT

SUMMARY

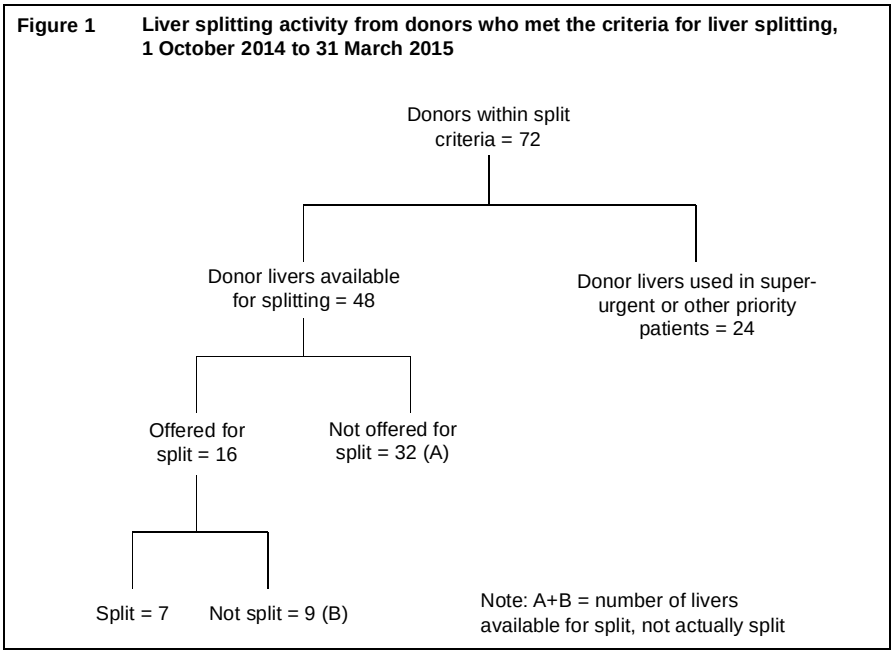
BACKGROUND

1 Donors after brain death (DBD) aged < 40 years, weighing > 50kg and known to have spent < five days in an intensive care unit 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 October 2014 to 31 March 2015. In a quarter of the 32 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. Nine 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.

Figure 1 **Liver splitting activity from donors who met the criteria for liver splitting, 1 October 2014 to 31 March 2015**



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 borderline evidence of superior survival for retained split livers (Log-rank test: p=0.05). 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 96%).

Kate Martin and Elisa Allen
April 2015

NHS BLOOD AND TRANSPLANT

LIVER ADVISORY GROUP

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 October 2014 and 31 March 2015 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 30 September 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 72 UK DBD donors whose liver was donated between 1 October 2014 and 31 March 2015 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 77 UK DBD whose liver was donated between 1 April and 30 September 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 October 2014 to March 2015, with April to September 2014 figures for comparison. Between 1 October 2014 and 31 March 2015, of the 72 DBD donors meeting the splitting criteria (77 between 1 April and 30 September 2014), 48 (67%) livers were available for splitting (54 (70%) between April and September 2014). Of these 48 livers, 16 (33%) were offered for splitting (24 of the 54 (44%) between April and September 2014). Of the 16 livers offered for splitting, 7 (44%) were actually split (9 of the 24 (38%) were split between April and September 2014). This activity is summarised in **Figure 1**.

Table 1 Donors meeting criteria for liver splitting, by donor allocation zone, 1 October 2014 to 31 March 2015 (1 April to 30 September 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 N_o		% of available		Split N_s		% of offered		Whole N_w		Reduced N_r	
Birmingham	15	(20)	5	(5)	1	(0)	9	(15)	3	(6)	33	(40)	0	(3)	0	(50)	3	(3)	0	(0)
Cambridge	11	(10)	4	(3)	0	(0)	7	(7)	2	(1)	29	(14)	2	(0)	100	(0)	0	(1)	0	(0)
Edinburgh	7	(11)	2	(2)	0	(0)	5	(9)	2	(5)	40	(56)	1	(3)	50	(60)	1	(2)	0	(0)
King's College	14	(11)	4	(5)	1	(1)	9	(5)	2	(1)	22	(20)	1	(1)	50	(100)	1	(0)	0	(0)
Leeds	12	(9)	2	(3)	1	(0)	9	(6)	1	(3)	11	(50)	0	(1)	0	(33)	1	(2)	0	(0)
Newcastle	4	(7)	0	(1)	0	(1)	4	(5)	3	(4)	75	(80)	1	(1)	33	(25)	2	(3)	0	(0)
Royal Free	9	(9)	2	(1)	2	(1)	5	(7)	3	(4)	60	(57)	2	(0)	67	(0)	1	(4)	0	(0)
TOTAL	**72**	**(77)**	**19[1]**	**(20[2])**	**5[3]**	**(3[4])**	**48**	**(54)**	**16**	**(24)**	**33**	**(44)**	**7**	**(9)**	**44**	**(38)**	**9**	**(15)**	**0**	**(0)**

[1] Three of these livers were split and used to transplant one super-urgent/ hepatoblastoma recipient and one elective liver only recipient
[2] Seven of these livers were split and used to transplant one super-urgent/ hepatoblastoma recipient and one elective liver only recipient
[3] One of these livers were split and used to transplant one multi-organ recipient and one elective liver only recipient
[4] None of these livers were split

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 72 livers resulted in 83 transplants, of which 13 (16%) were performed in paediatric patients (the 77 livers between April and September 2014 resulted in 93 transplants, 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 32 livers not being offered for splitting (78% of the 41 livers available for splitting that were not split). In 8 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 less than 50% of donors.

Table 2 Reasons given for why 32 livers from donors meeting the liver splitting criteria, between 1 October 2014 and 31 March 2015, 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	Abnormal liver function tests and raised sodium	102
2	Birmingham	Birmingham	Liver appeared fatty on ultrasound	24
3	Birmingham	Birmingham	Donor history of IV drug abuse	32
4	Birmingham	Birmingham	Over the centre's weight criteria for splitting	
5	Cambridge	Cambridge	Strength of Norad dose too high	
6	Cambridge	Cambridge	Abnormal liver function tests (ALT 123)	
7	Edinburgh	Edinburgh	Liver too small to be split	
8	Edinburgh	Leeds	Liver deemed unsuitable for splitting upon inspection	100
9	King's College	Birmingham	Marginal donor due to history/previous surgery/Marfan's syndrome/Function/Raised amylase and Gamm	
10	King's College	King's College	Extremely large liver, mildly fatty	21
11	King's College	King's College	Patchy perfusion and large (2.5kg)	
12	King's College	King's College	Hepatitis C positive donor	
13	King's College	King's College	At least 25% fatty and edematous	
14	King's College	Royal Free	Alcohol history. Abnormal liver function tests (Bilirubin 23, ALT 94, GGT 53)	
15	Leeds	Edinburgh	Donor BMI 40.4 and organ fatty.	
16	Leeds	Leeds	Marginal graft due to function (ALT 37)	103
17	Leeds	Leeds	Liver function tests (ALT 118)	83
18	Leeds	Leeds	Liver function tests (ALT 143)	
19	Leeds	Leeds	Raised ALT (462)	
20	Leeds	Leeds	Liver steatotic	
21	Newcastle	Birmingham	Donor medical history - drug abuse, fatty liver	
22	Royal Free	Royal Free	Mildly fatty and minimal fibrosis	
Recipient reasons				
23	Birmingham	Birmingham	Was due to be split but paediatric patient became ill	90
24	Royal Free	Royal Free	Third liver transplant for recipient	
Other reasons				
25	Birmingham	Birmingham	Timings - was offered to centre 2 hours post cross-clamp.	
26	Cambridge	Cambridge	Timings - was offered when already out of body	21
27	Cambridge	Cambridge	Very ill recipient needed the whole liver (surgeon agreed with Leeds, Kings and Birmingham)	
28	Cambridge	Newcastle	Received offer 15 minutes before cross clamp - there wasn't time to facilitate splitting	
29	Edinburgh	Edinburgh	SNOD wrongly informed by Duty Office liver outside splitting criteria (ITU stay)	21
30	King's College	King's College	Liver accepted for super urgent patient but not used due to AV malformation on liver	

Table 2 **Reasons given for why 32 livers from donors meeting the liver splitting criteria, between 1 October 2014 and 31 March 2015, were not offered for splitting**

Donor	Donor allocation zone	Transplanting centre	Reason for liver not being offered for splitting	AST (iu/l)
31	Leeds	Leeds	Donor unstable and recipient is large and needed a whole liver	
32	Leeds	Royal Free	Damage to artery incurred during retrieval	

10 The reasons given for not splitting the remaining 9 livers that were offered for splitting but were not split (22% of the 41 livers available for splitting that were not split) are detailed in **Table 3**.

Table 3 **Reasons given for why 9 livers from donors meeting the split liver criteria, between 1 October 2014 and 31 March 2015, that were offered for splitting were not split**

Donor	Donor allocation zone	Transplanting centre	Details of why liver was not split	AST (iu/l)
Donor reasons				
1	Birmingham	Birmingham	Left lateral offered and declined by all centres on past history/risk	
2	Leeds	Leeds	Left lateral accepted by King's and declined on inspection as fatty	
3	Newcastle	Leeds	Was due to be split but Birmingham declined left-lateral segment as too small	
Recipient reasons				
4	Birmingham	Birmingham	Left lateral offered and declined by all centres on past history/no suitable recipients	97
5	Birmingham	Birmingham	No suitable recipients and fatty organ	
6	Edinburgh	Edinburgh	Left lateral offered and declined on no suitable recipients/fatty organ/distance	
7	King's College	Edinburgh	Left lateral segment offered and declined due to virology and no suitable recipients for ABO	
8	Newcastle	Leeds	Left lateral segment offered and declined by all centres for logistical/capacity reasons.	33
9	Royal Free	Royal Free	Left lateral segment declined due to no suitable recipients and a medical history of astrocytoma	

11 There were 2 liver transplant recipients with Hepatoblastoma who were transplanted from a DBD donor between 6 October 2014 and 31 March 2015. Of these 1 was a split liver transplant, and 1 was a whole liver transplant. Details of these transplants are in **Table 4**.

Table 4 Details of Hepatoblastoma patients transplanted between 6 October 2014 and 31 March 2015

Donor	Transplanting centre	Transplant type	Donor age (years)	Recipient age (years)	Reason for not splitting
1	Birmingham	Whole	49	17	Donor age exceeds criteria for splitting
2	Birmingham	Split	15	2	

Note: On 6 October 2014 it became a requirement to split livers, within criteria for splitting, offered to Hepatoblastoma patients

TRANSPLANT SURVIVAL

Data and methods

12 Data on 717 NHS group 1 first elective split liver only transplants in the UK using livers from DBD donors between 1 April 2006 and 30 September 2014 were analysed. Auxiliary and intestinal transplants were excluded from this cohort as were regrafts. Follow-up data were as recorded on the UKTR on 6 April 2015.

13 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 57% 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 59% 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).

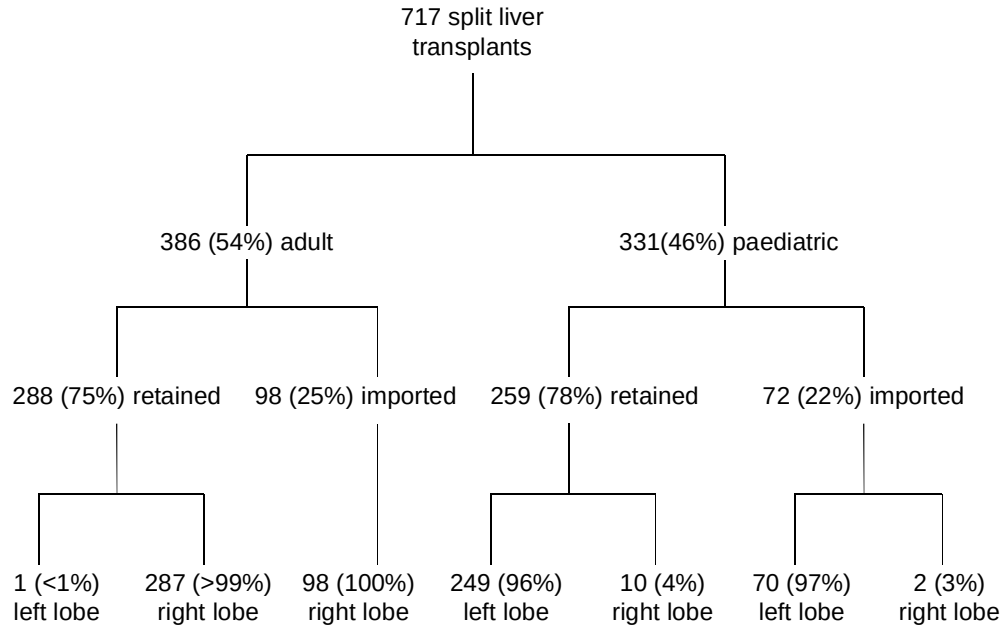
14 Survival up to five years post-split liver transplant was compared for “retained” and “imported” split livers and for “adult unit surgeon” and “paed unit surgeon” split livers, separately for adult and paediatric patients. These analyses were performed using the Kaplan-Meier estimation method and 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.

15 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 3,418 NHS group 1 first adult elective patients transplanted in the UK between 1 April 2006 and 30 September 2014. A sub-group analysis was performed on just those transplants performed between 1 April 2010 and 30 September 2014 (N=1,939). Again, auxiliary and multi-organ transplants and regrafts were excluded and follow-up data were as recorded on the UKTR on 6 April 2015.

Results

16 **Figure 2** shows a breakdown of the 717 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 and 30 September 2014



17 **Table 5** shows a breakdown of the 717 split liver transplants by recipient age group, transplant centres and whether the liver was retained or imported.

Table 5 NHS group 1 first elective split liver only transplants in the UK using livers from donors after brain death, 1 April 2006 – 30 September 2014

Transplant centre	Retained N	Imported N	Total
Paediatric recipients			
Birmingham	100	19	119
King's College	116	40	156
Leeds	43	13	56
Total	**259**	**72**	**331**
Adult recipients			
Birmingham	117	5	122
Cambridge	13	14	27
Edinburgh	21	41	62
King's College	88	4	92
Leeds	36	8	44
Newcastle	4	10	14
Royal Free	9	16	25
Total	**288**	**98**	**386**
TOTAL	**547**	**170**	**717**

18 **Table 6** 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=13)). 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 6 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 30 September 2014

	N[1]	CIT (hours)	
		Median	Range
Left lobes transplanted in paediatric patients			
Retained	198	9.0	3.6 – 16.2
Imported	57	11.7	2.9 – 16.5
Right lobes transplanted in adult patients			
Retained	270	9.7	3.9 – 17.6
Imported	94	12.4	6.6 – 16.3

[1] CIT was not reported for a total of 85 split livers

Unadjusted survival analysis

19 **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 83%. The log-rank test showed no statistical difference in the overall survival curves in the paediatric analysis (p=0.9). Contrastingly, there was a borderline significant difference between the survival curves in the adult analysis (p=0.05). The estimated five year transplant survival rates for imported and split livers were approximately 70% and 80% but there was some overlap in confidence intervals (57%-80% and 74%-85%, respectively).

20 **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 analyses. The estimated five year transplant survival rates for livers split by adult unit surgeons and livers split by paediatric unit surgeons were approximately 81% (60%-92%) and 84% (78%-88%), respectively, for paediatric patients and 81% (65%-90%) and 78% (72%-82%), respectively, for adult patients.

21 Causes of graft failure or patient death that were reported to the UKTR for the 121 out of 717 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 30 September 2014**

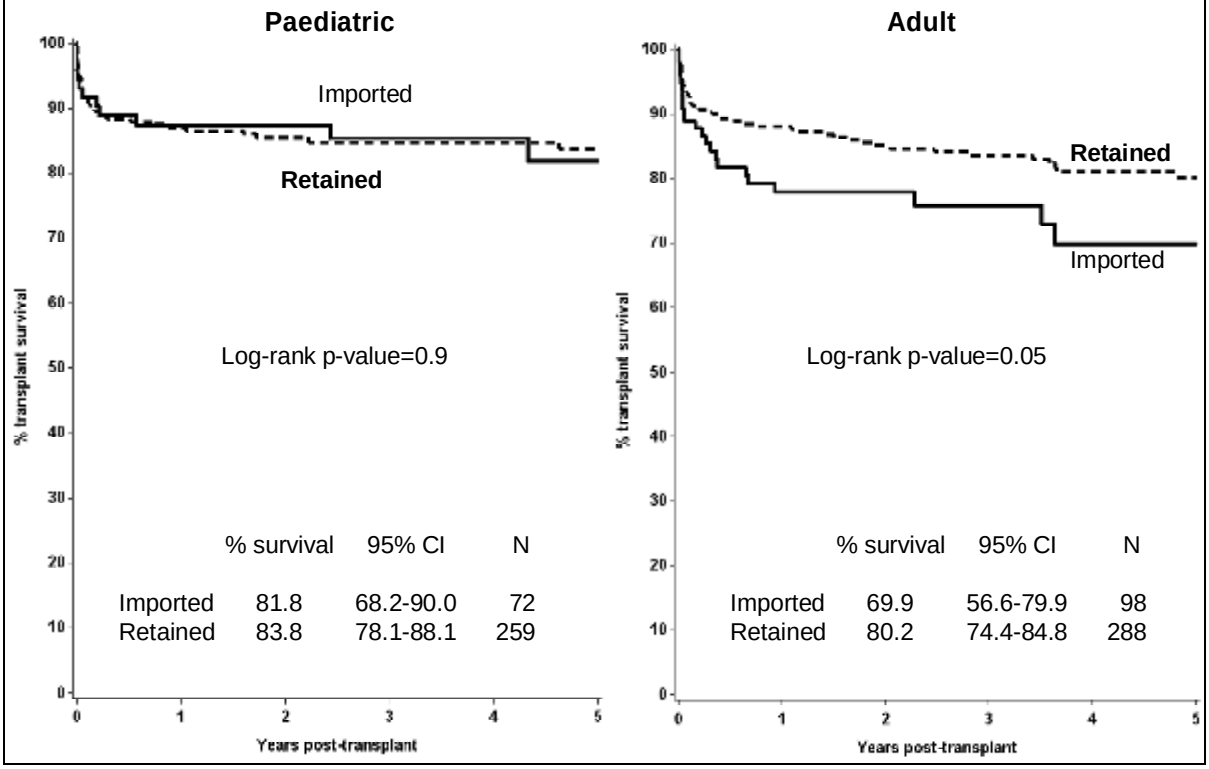
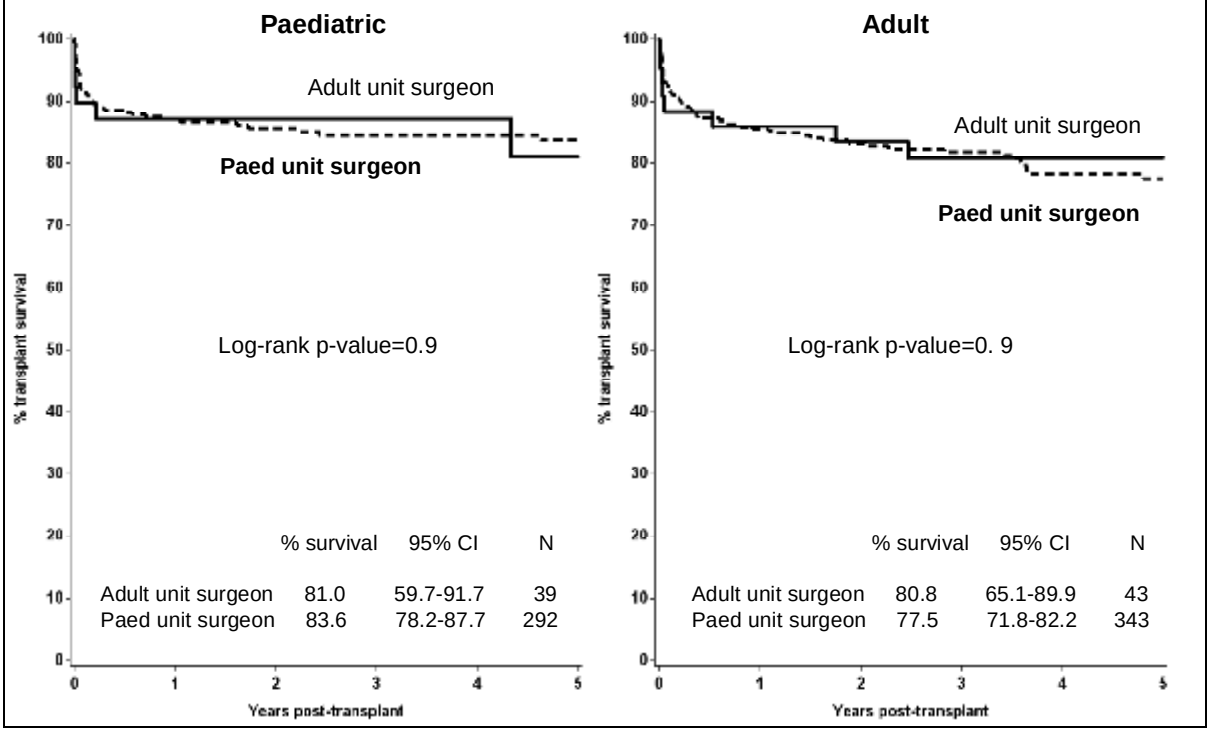
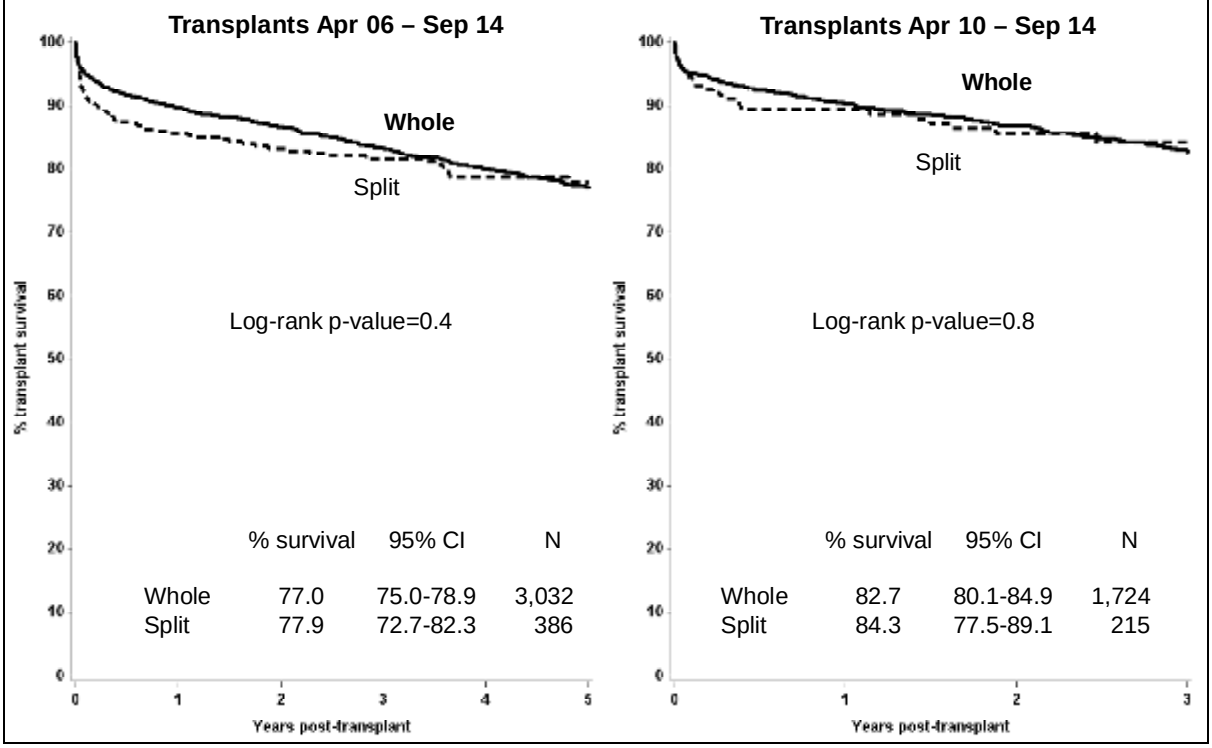


Figure 4 **Comparison of five year transplant survival of livers split by adult and paediatric unit surgeons, transplanted in NHS group 1 elective patients in the UK between 1 April 2006 and 30 September 2014**



22 **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 30 September 2014 and up to three years for whole and split liver transplants in the reduced cohort of 1 April 2010 to 30 September 2014. For transplants between April 2006 and September 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 September 2014, there is no difference in the unadjusted survival curves at three years post-transplantation (p=0.8).

Figure 5 Comparison of five and three year transplant survival of whole and split livers transplanted in NHS group 1 elective adult patients in the UK between 1 April 2006 and 30 September 2014 and 1 April 2010 and 30 September 2014



23 Data on 36 NHS group 1 first super urgent split liver only transplants in the UK using livers from DBD donors between 1 April 2006 and 30 September 2014 were also analysed. Auxiliary and intestinal transplants were excluded from this cohort as were regrafts. Follow-up data were as recorded on the UKTR on 9 April 2015. Of these there were 9 (29%) deaths or failed grafts in the 31 paediatric recipients, and 2 (40%) deaths or failed grafts in the 5 adult recipients. Due to these small numbers no survival analysis could be performed.

SUMMARY

24 There were 72 livers donated between 1 October 2014 and 31 March 2015 from donors who met the criteria for liver splitting (6% fewer than previous six months, Apr-Sep 2014). Of these, 48 (67%) were available for splitting for elective recipients, having not been used in super-urgent, hepatoblastoma, intestinal or multi-organ recipients. Of these, 16 (33%) were offered for splitting and 7 (44% of the 16) were actually split (22% fewer than previous six months, Apr-Sep 2014). In a quarter of the 32 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. Nine 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 paediatric patients for the left lateral segment.

25 An unadjusted analysis of survival following split liver transplantation, comparing retained and imported split livers transplanted between 1 April 2006 and 30 September 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 borderline evidence of superior survival for retained split livers (p=0.05). 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.

26 A comparison of unadjusted survival estimates following whole and split liver transplantation in adult patients, between 1 April 2006 and 30 September 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

27 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 96%).

28 This paper now includes details of all liver transplant recipients with Hepatoblastoma, transplanted within the 6 months reported on. This is due to the new requirement in place from 6 October 2014 stating that all within-criteria livers offered to Hepatoblastoma patients must be considered for splitting.

Kate Martin and Elisa Allen
Statistics and Clinical Studies **April 2015**

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 30 September 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	Imported split liver	Liver split by paediatric unit surgeon	Liver split by adult unit surgeon	Total
	N	N	N	N	N
PAEDIATRIC PATIENTS					
Cause of graft failure - patient did not die					
Hepatic artery thrombosis	12	3	13	2	15
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	**21**	**6**	**23**	**4**	**27**
Cause of death					
Multi-system failure	5	2	7	0	7
Haemorrhage	1	2	2	1	3
Primary non-function -> multi-system failure	3	0	3	0	3
Septicaemia	1	0	1	0	1
Recurrent disease	1	0	1	0	1
Other	6	0	6	0	6
Not reported	0	1	0	1	1
Total	**17**	**5**	**20**	**2**	**22**
TOTAL	**38**	**11**	**43**	**6**	**49**
ADULT PATIENTS					
Cause of graft failure - patient did not die					
Hepatic artery thrombosis	12	5	14	3	17
Other	5	3	7	1	8
Total	**17**	**8**	**21**	**4**	**25**
Cause of death					
Multi-organ failure	5	5	9	1	10
Hepatic artery thrombosis -> multi-system failure/myocardial infarction/pulmonary infection	4	4	7	1	8
Non-lymphoid malignant disease	5	1	6	0	6
Non-thrombotic infarction -> multi-system failure/septicaemia	4	0	4	0	4
Recurrent disease	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	3	3	5	1	6
Not reported	2	1	3	0	3
Total	**32**	**15**	**43**	**4**	**47**
TOTAL	**49**	**23**	**64**	**8**	**72**