

NHS BLOOD AND TRANSPLANT**BOWEL ADVISORY GROUP****FACTORS AFFECTING SURVIVAL FOLLOWING INTESTINE TRANSPLANTATION****SUMMARY****INTRODUCTION**

- 1 This paper provides an update on the work that has been carried out on behalf of the Bowel Advisory Group (BAG) to identify factors that affect patient outcomes following intestine transplantation. Preliminary investigations were presented at the previous BAG meeting (BAG(14)26).
- 2 This work is due to be presented at the forthcoming British Transplantation Society Congress (March 2015) and has been submitted to the International Small Bowel Transplant Symposium (June 2015).

DATA ANALYSIS

- 3 113 intestine transplants performed in first-time recipients in the UK between 1 April 2008 and 31 December 2014 were analysed. 68 (60%) transplants were in adult recipients and 45 (40%) were in paediatric recipients. The analysis was performed separately for adults and paediatrics due to the heterogeneity of these two cohorts.
- 4 Over 40 recipient, donor and transplant related variables were considered in the analysis and both univariate and multivariate tests were performed. Two survival outcomes were analysed; three year patient survival and three year transplant survival, where either death or re-registration within three years were classed as events in the latter outcome.
- 5 In the adult cohort, several variables were significantly associated with patient survival and/or transplant survival on their own, including recipient ethnic group, restricted vein access, recipient age and liver transplanted yes/no. However, when considered in combination, there was evidence to suggest that just UK End-stage Liver Disease score, ethnic group and donor-recipient BMI mismatch are sufficient to explain adult survival data, of the variables considered. Moreover, there was some modest evidence that non-white ethnicity and a BMI mismatch of at least three units (where donor BMI > recipient BMI) are associated with poorer outcomes.
- 6 Multivariate analysis was not possible in the paediatric cohort due to a small number of events. In the univariate analysis, the most significant individual predictor of three year patient survival was recipient age, where older age at transplant was mildly associated with a reduced risk of death and there was also some weak evidence that longer cold ischaemic time was associated with poorer outcomes.

RECOMMENDATIONS

- 7 Members are asked to provide feedback on the work that has been carried out so far. As the cohort of transplanted patients since 2008 is small the results presented so far should not be viewed as conclusive. It may be interesting to look at survival from the point of registration onto the national intestine transplant list as this would offer a larger cohort in which to understand risk-factors in this patient group.

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NHS BLOOD AND TRANSPLANT

BOWEL ADVISORY GROUP

FACTORS AFFECTING SURVIVAL FOLLOWING INTESTINE TRANSPLANTATION

INTRODUCTION

- 1 This paper provides an update on the work that has been carried out on behalf of the Bowel Advisory Group (BAG) to identify factors that affect patient outcomes following intestine transplantation. Preliminary investigations were presented at the previous BAG meeting (BAG(14)26).
- 2 This work is due to be presented at the forthcoming British Transplantation Society Congress (March 2015) and has been submitted to the International Small Bowel Transplant Symposium (June 2015).

DATA AND METHODS

- 3 Detailed national data collection on intestine transplant candidates and recipients has only been in place since 2008 so in order to investigate factors affecting survival, 113 intestine transplants performed in first-time recipients in the UK between 1 April 2008 and 31 December 2014 were analysed. 68 (60%) transplants were in adult recipients and 45 (40%) were in paediatric recipients. The analysis was performed separately for adults and paediatrics due to the heterogeneity of these two cohorts.
- 4 Over 40 recipient, donor and transplant related variables were considered in the analysis, including recipient age, donor age, transplant type, indication for transplant, restricted vein access and other pre-transplant comorbidities. Any missing data at the point of transplantation were substituted with data recorded at registration if equivalent. Simple imputation techniques were used where missing data was less than 10% and missing categories were used otherwise. Some variables were considered in both continuous and categorical forms.
- 5 Two survival outcomes were analysed; the first of which was three year patient survival where patient deaths within three years post-transplant were classed as events and patient survival times greater than three years were censored at three years. The second outcome was a surrogate for three year transplant survival, where any patient deaths or re-registrations onto the national intestine transplant list within three years post-transplant were classed as events. If a patient was re-registered before death or before their most recent survival date, their survival time ended at the date of re-registration. All follow-up data were extracted from the UK Transplant Registry (UKTR) on 11 January 2015. For paediatric patients, transplant survival was only slightly different to patient survival (as just one patient was re-registered within three years and they died a few days later) so the results of the patient survival analysis only are presented in this paper.
- 6 The first step was to investigate the effect of each variable individually on survival times. This was done using a Cox proportional hazards regression model with only one variable present. The change in $-2\text{Log}[\text{Likelihood}]$ from a model with no explanatory variables was tested to see if the variable in question explained any of the variation in survival times. If the test for this change (the Likelihood Ratio Test: LRT) provided a p-value of ≤ 0.1 then that variable was considered to have some significant effect on survival times, individually.
- 7 The next step was to build a multivariate model that included only those variables that remained significant in the presence of each other. This was done with caution due to the small number of events and the danger of over-fitting. This step could not be taken for the paediatric cohort for these reasons. In the adult cohort, a stepwise variable selection

method was used to build models for three year patient and transplant survival, separately (where the LRT was used to compare nested models). As these two survival outcomes are very similar, combined evidence from the two models was used to form the final models. As there were more events in the transplant survival model, the evidence from this model was deemed more reliable.

RESULTS

- 8 **Appendix I** shows summary statistics and univariate LRT p-values for the variables considered in the adult only analysis. Several variables were significantly associated with patient survival and/or transplant survival on their own (see bold p-values), including recipient ethnic group, restricted vein access, recipient age and liver transplanted yes/no. However, when considered in combination, there was evidence to suggest that just UK End-stage Liver Disease score (UKELD), ethnic group and donor-recipient BMI mismatch are sufficient to explain adult survival data, of the variables considered. Moreover, there was some modest evidence that non-white ethnicity and a BMI mismatch of at least three units (where donor BMI > recipient BMI) are associated with poorer outcomes (see **Table 1** and **Table 2** for multivariate Cox proportional hazards model results for three year adult patient survival and transplant survival, respectively). Note that checks on the adequacy of these models are yet to be conducted; hence these results should not be viewed as conclusive.

Table 1 Results of the multivariate Cox proportional hazards regression model for the risk of death within three years of intestine transplantation for adult patients					
Term	Level	Hazard Ratio estimate	95% HR confidence limits		LRT p-value
Recipient UKELD score	0-49	1.00	-	-	0.06
	50-54	2.39	0.66	8.66	
	55+	2.08	0.55	7.87	
	Missing	0.57	0.15	2.07	
Recipient ethnic group	White	1.00	-	-	0.02
	Non-white	4.88	1.48	16.04	
Donor-recipient BMI match	Donor BMI at least 3 units higher than recipient BMI	2.37	0.97	5.83	0.07
	Otherwise	1.00	-	-	

Table 2 Results of the multivariate Cox proportional hazards regression model for the risk of death or re-registration within three years of intestine transplantation for adult patients					
Term	Level	Hazard Ratio estimate	95% HR confidence limits		LRT p-value
Recipient UKELD score	0-49	1.00	-	-	0.007
	50-54	3.75	1.22	11.52	
	55+	1.72	0.49	6.03	
	Missing	0.66	0.21	2.09	
Recipient ethnic group	White	1.00	-	-	0.03
	Non-white	4.44	1.38	14.28	
Donor-recipient BMI match	Donor BMI at least 3 units higher than recipient BMI	2.48	1.08	5.74	0.04
	Otherwise	1.00	-	-	

- 9 **Appendix II** shows summary statistics and univariate LRT p-values for the variables considered in the paediatric only analysis. The most significant individual predictor of three year patient survival in paediatrics was recipient age, where older age at transplant was mildly associated with a reduced risk of death. There was also some weak evidence that longer cold ischaemic time was associated with poorer outcomes. Multivariate analysis was not possible in the paediatric cohort due to a small number of events.
- 10 For information, the follow-up data recorded on the UKTR for these cohorts provided overall unadjusted survival rate estimates of 62% (95% CI: 47%-73%) for adult three year patient survival, 52% (95% CI: 37%-64%) for adult three year transplant survival and 82% (95% CI: 66%-91%) for paediatric three year patient survival.

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Appendix I – Summary statistics and univariate Likelihood Ratio Test (LRT) p-values for variables considered in the analysis of adult survival times following intestine transplantation

Factor	Level	TOTAL	Deaths within 3 years (N=22)		LRT p-value	Deaths or re-registrations within 3 years (N=28)		LRT p-value
RECIPIENT FACTORS		N	N	%		N	%	
Age group (years)	18-39	25	5	20.0	0.3	7	28.0	0.3
	40-49	19	7	36.8		10	52.6	
	50+	24	10	41.7		11	45.8	
Sex	Male	37	12	32.4	0.9	16	43.2	0.9
	Female	31	10	32.3		12	38.7	
Ethnic group	Non-white	6	4	66.7	0.07	4	66.7	0.1
	White	62	18	29.0		24	38.7	
Indication for tx	Short bowel syndrome	38	11	28.9	0.7	15	39.5	0.4
	Motility disorders	8	3	37.5		3	37.5	
	Malignancy	7	2	28.6		2	28.6	
	Liver disease	7	2	28.6		3	42.9	
	Other/missing	8	4	50.0		5	62.5	
In-patient status	Out-patient	52	17	32.7	0.5	20	38.5	0.07
	In-patient	16	5	31.3		8	50.0	
Previous abdominal surgery	No	5	1	20.0	0.5	3	60.0	0.4
	Yes	63	21	33.3		25	39.7	
Restricted vein access	No	42	17	40.5	0.07	21	50.0	0.06
	Yes	19	4	21.1		5	26.3	
	Missing	7	1	14.3		2	28.6	
Vein access group	No restricted veins	42	17	40.5	0.3	21	50.0	0.2
	1 vein not patent	4	1	25.0		1	25.0	
	2 veins not patent	6	1	16.7		1	16.7	
	3+ veins not patent	9	2	22.2		3	33.3	
	Missing	7	1	14.3		2	28.6	
Super-urgent	No	65	21	32.3	0.8	26	40.0	0.2
	Yes	3	1	33.3		2	66.7	
Opiate usage	Previous	13	6	46.2	0.2	7	53.8	0.1
	Current	24	8	33.3		11	45.8	
	None	12	5	41.7		6	50.0	
	Missing	19	3	15.8		4	21.1	
History of malignancy (uses question at reg and indication for tx)	No	58	18	31.0	0.7	24	41.4	0.8
	Yes	10	4	40.0		4	40.0	
Comorbidities (if prior cardiac disease, current angina, cerebrovascular disease, symptomatic peripheral vascular disease, hypertension, diabetes or smoking)	No	33	11	33.3	0.96	13	39.4	0.7
	Yes	35	11	31.4		15	42.9	
Comorbidity count (see above)	0	33	11	33.3	0.4	13	39.4	0.8
	1	26	7	26.9		11	42.3	
	2 or more	9	4	44.4		4	44.4	
Serious line infection needing ICU admission	No	48	18	37.5	0.1	22	45.8	0.2
	Yes	11	3	27.3		4	36.4	
	Missing	9	1	11.1		2	22.2	
On total parenteral nutrition (TPN)	No	9	2	22.2	0.3	4	44.4	0.7
	Yes	52	19	36.5		22	42.3	
	Missing	7	1	14.3		2	28.6	
TPN group	Not on TPN	9	2	22.2	0.6	4	44.4	0.9
	1-12 hours TPN/day	23	9	39.1		10	43.5	
	More than 12 hours TPN/day	16	5	31.3		6	37.5	
	On TPN, hours missing	13	5	38.5		6	46.2	
	Missing	7	1	14.3		2	28.6	
Registration comorbidities (if chronic lung disease, history of intestinal dysmotility or presence of other coexisting systemic disorders at reg)	No	45	17	37.8	0.2	22	48.9	0.09
	Yes	10	2	20.0		2	20.0	
	Missing	13	3	23.1		4	30.8	
Clinical status pre-tx indicator (if ventilated, renal support, ascites, diuretic therapy, oesophageal varices, stomal varices, variceal haemorrhage, inotrope therapy, spont bacterial peritonitis, sepsis within last 24hr or encephalopathic)	No	26	9	34.6	0.09	11	42.3	0.06
	Yes	26	11	42.3		14	53.8	
	Missing	16	2	12.5		3	18.8	
Lifestyle activity score	1 or 2	10	2	20.0	0.2	3	30.0	0.1
	3	41	12	29.3		15	36.6	
	4 or 5	17	8	47.1		10	58.8	
UKELD group	0-49	16	4	25.0	0.1	5	31.3	0.04
	50-54	15	7	46.7		10	66.7	
	55+	12	5	41.7		5	41.7	
	Missing	25	6	24.0		8	32.0	
Bilirubin group (umol/l)	0-99	63	20	31.7	0.6	26	41.3	0.9
	100-200	5	2	40.0		2	40.0	

Factor	Level	TOTAL	Deaths within 3 years		LRT p-value	Deaths or re-		LRT p-value
RECIPIENT FACTORS		N	N	%		N	%	
Sodium group (mmol/l)	0-136	20	12	60.0	0.005	12	60.0	0.04
	137-138	16	4	25.0		7	43.8	
	139+	19	4	21.1		6	31.6	
	Missing	13	2	15.4		3	23.1	
INR group	0-1.1	18	5	27.8	0.7	7	38.9	0.3
	1.2-1.4	16	5	31.3		8	50.0	
	1.5+	20	8	40.0		9	45.0	
	Missing	14	4	28.6		4	28.6	
Waiting time to tx	< 90 days	48	16	33.3	0.9	22	45.8	0.6
	90 days - half a year	6	2	33.3		2	33.3	
	half a year - 1 year	9	3	33.3		3	33.3	
	1 - 2 years	5	1	20.0		1	20.0	
		N	Median	Range		Median	Range	
Age (years)		68	45.5	18.0-73.0	0.09	45.5	18.0-73.0	0.1
Bilirubin (umol/l)		68	14.0	2.0-421.0	0.5	14.0	2.0-421.0	0.3
Creatinine (mmol/l)		68	76.0	28.0-270.0	0.8	76.0	28.0-270.0	0.9
BMI		68	21.1	14.1-29.6	0.3	21.1	14.1-29.6	0.2
Height (cm)		68	170.0	137.0-185.0	0.7	170.0	137.0-185.0	0.4
Weight (kg)		68	61.2	26.5-97.0	0.5	61.2	26.5-97.0	0.6
		N	N	%		N	%	
DONOR FACTORS		N	N	%		N	%	
Sex	Male	27	11	40.7	0.2	12	44.4	0.7
	Female	41	11	26.8		16	39.0	
Cause of death	Stroke	33	12	36.4	0.06	14	42.4	0.5
	Trauma	18	8	44.4		9	50.0	
	Other	17	2	11.8		5	29.4	
Ethnic group	Non-white	2	1	50.0	0.9	2	100.0	0.4
	White	66	21	31.8		26	39.4	
		N	Median	Range		Median	Range	
Age (years)		68	32.0	9.0-57.0	0.5	32.0	9.0-57.0	0.4
BMI		68	21.5	15.2-27.8	0.2	21.5	15.2-27.8	0.2
Height (cm)		68	170.0	139.0-191.0	0.7	170.0	139.0-191.0	0.8
Weight (kg)		68	61.0	31.6-85.0	0.3	61.0	31.6-85.0	0.3
		N	N	%		N	%	
TRANSPLANT FACTORS		N	N	%		N	%	
Centre	Cambridge	43	13	30.2	0.7	18	41.9	0.6
	Oxford	25	9	36.0		10	40.0	
Cold ischaemic time (mins)	0-299	15	7	46.7	0.1	8	53.3	0.4
	300-359	12	2	16.7		4	33.3	
	360+	16	8	50.0		9	56.3	
	Missing	25	5	20.0		7	28.0	
Imported	No	66	22	33.3	0.2	28	42.4	0.1
	Yes	2	0	0.0		0	0.0	
Tx type	BO	27	6	22.2	0.2	8	29.6	0.08
	LBP or MV	26	11	42.3		14	53.8	
	MMV	15	5	33.3		6	40.0	
Liver txd	No	42	11	26.2	0.1	14	33.3	0.04
	Yes	26	11	42.3		14	53.8	
Donor-recipient blood group match	Identical	58	19	32.8	0.8	24	41.4	0.8
	Compatible	10	3	30.0		4	40.0	
Donor-recipient BMI match	Donor BMI at least 3 units	16	8	50.0	0.06	9	56.3	0.09
	Otherwise	52	14	26.9		19	36.5	
Donor-recipient CMV match	No	36	10	27.8	0.3	13	36.1	0.3
	Yes	32	12	37.5		15	46.9	
Donor-recipient sex match	No	40	9	22.5	0.1	14	35.0	0.5
	Yes	28	13	46.4		14	50.0	
Donor-recipient ethnicity match	Both white	60	17	28.3	0.1	22	36.7	0.07
	Otherwise	8	5	62.5		6	75.0	

Appendix II – Summary statistics and univariate Likelihood Ratio Test (LRT) p-values for variables considered in the analysis of paediatric survival times following intestine transplantation

Factor	Level	TOTAL (N=45)	Deaths within 3 years (N=7)		LRT p-value
RECIPIENT FACTORS		N	N	%	
Age group (years)	0-1	16	5	31.3	0.2
	2-4	15	1	6.7	
	5-9	11	1	9.1	
	10+	3	0	0.0	
Sex	Male	24	3	12.5	0.5
	Female	21	4	19.0	
Ethnic group	Non-white	8	0	0.0	0.1
	White	37	7	18.9	
Indication for tx	Short bowel syndrome	22	3	13.6	0.9
	Motility disorders	10	2	20.0	
	Primary mucosal disorders or liver disease	5	1	20.0	
	Other/missing	8	1	12.5	
In-patient status	Out-patient	40	6	15.0	0.7
	In-patient	5	1	20.0	
Previous abdominal surgery	No	5	1	20.0	0.8
	Yes	40	6	15.0	
Restricted vein access	No	14	3	21.4	0.5
	Yes	21	2	9.5	
	Missing	10	2	20.0	
Vein access group	No restricted veins	14	3	21.4	0.6
	1 vein not patent	8	1	12.5	
	2 veins not patent	6	0	0.0	
	3+ veins not patent	7	1	14.3	
	Missing	10	2	20.0	
Opiate usage	Previous	23	3	13.0	0.6
	None	15	2	13.3	
	Missing	7	2	28.6	
Comorbidities (if prior cardiac disease, current angina, cerebrovascular disease, symptomatic peripheral vascular disease, hypertension, diabetes or smoking)	No	36	5	13.9	0.4
	Yes	3	0	0.0	
	Missing	6	2	33.3	
Premature birth	No	19	1	5.3	0.2
	Yes	19	4	21.1	
	Missing	7	2	28.6	
Serious line infection needing ICU admission	No	24	4	16.7	0.6
	Yes	13	1	7.7	
	Missing	8	2	25.0	
TPN group	0-12 hours TPN/day	22	2	9.1	0.4
	More than 12 hours TPN/day	15	3	20.0	
	Missing	8	2	25.0	
Registration comorbidities (if chronic lung disease, history of intestinal dysmotility or presence of other coexisting systemic disorders at reg)	No	14	2	14.3	0.8
	Yes	23	3	13.0	
	Missing	8	2	25.0	
Clinical status pre-tx indicator (if ventilated, renal support, ascites, diuretic therapy, oesophageal varices, stomal varices, variceal haemorrhage, inotrope therapy, spont bacterial peritonitis, sepsis within last 24hr or encephalopathic)	No	23	3	13.0	0.6
	Yes	15	2	13.3	
	Missing	7	2	28.6	
UKELD group	0-45	9	0	0.0	0.2
	46-49	9	1	11.1	
	50+	10	1	10.0	
	Missing	17	5	29.4	
Bilirubin group (umol/l)	0-99	35	5	14.3	0.9
	100-199	7	1	14.3	
	200+	3	1	33.3	
INR group	0-1	6	0	0.0	0.1
	1.1-1.2	15	2	13.3	
	1.3+	7	0	0.0	
	Missing	17	5	29.4	
Waiting time to tx	< 90 days	12	2	16.7	0.95
	90 days - half a year	11	2	18.2	
	half a year - 1 year	22	3	13.6	
		N	Median	Range	
Age (years)		45	3.0	0.0-16.0	0.06
Bilirubin (umol/l)		45	9.5	1.0-644.0	0.5
Creatinine (mmol/l)		45	19.5	1.5-131.0	0.7
BMI		45	17.7	8.4-38.9	0.1
Height (cm)		45	83.5	54.0-155.0	0.4
Weight (kg)		45	12.6	5.5-57.0	0.09
Sodium (mmol/l)		45	137.0	128.0-151.0	0.2

Factor	Level	TOTAL (N=45)	Deaths within 3 years (N=7)		LRT p-value
DONOR FACTORS		N	N	%	
Sex	Male	26	3	11.5	0.4
	Female	19	4	21.1	
Cause of death	Stroke	10	1	10.0	0.8
	Trauma	10	2	20.0	
	Other	25	4	16.0	
Ethnic group	Non-white	4	1	25.0	0.7
	White	41	6	14.6	
		N	Median	Range	
Age (years)		45	4.0	0.0-43.0	0.6
BMI		45	15.6	10.0-25.7	0.3
Height (cm)		45	110.0	49.0-178.0	0.9
Weight (kg)		45	18.0	3.0-70.0	0.5
TRANSPLANT FACTORS		N	N	%	
Centre	Birmingham	32	6	18.8	0.5
	King's College	13	1	7.7	
Cold ischaemic time (mins)	0-449	24	1	4.2	0.07
	450+	11	3	27.3	
	Missing	10	3	30.0	
Imported	No	43	7	16.3	0.4
	Yes	2	0	0.0	
Tx type	BO	20	3	15.0	0.9
	LBP or MV	21	3	14.3	
	MMV	4	1	25.0	
Liver txd	No	24	4	16.7	0.9
	Yes	21	3	14.3	
Donor-recipient blood group match	Identical	39	7	17.9	0.2
	Compatible	6	0	0.0	
Donor-recipient BMI match	Donor BMI at least 3 units higher than recipient BMI	4	1	25.0	0.8
	Otherwise	41	6	14.6	
Donor-recipient CMV match	No	21	2	9.5	0.6
	Yes	18	4	22.2	
	Missing	6	1	16.7	
Donor-recipient sex match	No	24	2	8.3	0.2
	Yes	21	5	23.8	
Donor-recipient ethnicity match	Both white	33	6	18.2	0.5
	Otherwise	12	1	8.3	