LONG-TERM OUTCOMES OF LIVER TRANSPLANT RECIPIENTS FOLLOWED UP IN NON-TRANSPLANT CENTRES: CARE CLOSER TO HOME

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ABSTRACT

Introduction: Increasing rates of liver transplantation and improved outcomes have led to greater numbers of transplant recipients followed up in non-transplant centres. Our aim was to document long-term clinical outcomes of liver transplant recipients managed in this 'hub and spoke' healthcare model.

Methods: A retrospective analysis of all adult patients who underwent liver transplantation between 1987 and 2016, with post-transplant follow-up in two non-transplant centres in the UK (Nottingham) and Canada (Ottawa) was performed.

Results: The 1-, 5-, 10- and 20-year patient survival rates were 98%, 95%, 87% and 62%, and 100%, 96%, 88% and 62% in the Nottingham and Ottawa groups, respectively (p=0.87). There were no significant differences between the two centres in 1-, 5-, 10- and 20-year cumulative incidence of death-censored graft-survival (p=0.10), end-stage renal disease (p=0.29) or de novo cancer (p=0.22). Nottingham had a lower incidence of major cardiovascular events (p=0.008).

Conclusion: Adopting a new model of healthcare provides a means of delivering post-transplant patient care close to home, without compromising patient survival and long-term clinical outcomes.

KEYWORDS

Liver transplantation
Long-term outcomes
Non-transplant centres
Hub and spoke model

ABBREVIATIONS

AFP	α-fetoprotein
ALF	acute liver failure
CIHI	Canadian Institute for Health Information
CVE	cardiovascular events
DM	diabetes mellitus
ESRD	end-stage renal disease
HCC	hepatocellular carcinoma
IQR	interquartile range
LT	liver transplantation
MELD	model for end-stage liver disease score
NHSBT	National Health Service Blood and Transplant
SVR	sustained virologic response
TTV	Total Tumour Volume
UKELD	United Kingdom end-stage liver disease score

INTRODUCTION

Liver transplantation (LT) remains the only lifesaving treatment option for patients with end stage liver disease, acute liver failure (ALF), and selected patients with hepatocellular carcinoma (HCC) in whom other curative treatment options have failed or are not suitable. Over the past 10 years, rates of liver transplantation have increased by more than 25% in Canada (14.4 transplants per million; Canadian Institute for Health Information, CIHI) and 40% in the UK (15.2 transplants per million; National Health Service Blood and Transplant, NHSBT). Outcomes following LT have also improved substantially. Survival rates of >90%, 85%, and 70% at 1-, 5-, and 10-years post-LT, respectively, have become the accepted norm around the world [1-3].

More transplants and improved long-term outcomes have led to greater numbers of patients living with liver transplant. In 2018, there were more than 10,100 and 5,900 recipients living with liver transplant in the UK and Canada, respectively. The UK has seven liver transplant centres (0.1 per million), the same number as Canada (0.18 per million), although Canada's population is spread over nearly 10 million square kilometres. In both countries, many liver transplant recipients are followed at non-transplant centres, and these numbers are likely to continue to grow in future due to constraints of both population size and density.

A 'hub and spoke' model of healthcare, where secondary care establishments route patients to a specialised centre for specific services, and receive training, advice, and support in return, have been shown to improve patient access to excellent care [4, 5]. The UK has a more formal 'hub and spoke' model of delivering transplant care at non-transplant centres than Canada [6]. This study aims to document the long-term outcomes of patients followed up in non-transplant centres in the UK and Canada in order to inform future policy guidelines.

METHODS

STUDY POPULATION

This was a retrospective analysis of data from two tertiary care, non-transplant centres in the UK and Canada. All adult patients who underwent LT between 01 January 1987 and 31 December 2016, and followed up in either Nottingham University Hospital (UK) or The Ottawa Hospital (Canada) were eligible for inclusion. Those who underwent LT at <18 years of age and those who underwent combined organ transplantation were excluded. Data were extracted from electronic records and supplemented with manual chart review. This study was approved by the Nottingham University Hospitals Trust Clinical Effectiveness Board (19-416C) and the Ottawa Health Science Network Research Ethics Board Protocol (REB #20170905-01H).

LIVER TRANSPLANTATION SELECTION AND POST-TRANSPLANT FOLLOW-UP

Selection of patients in Nottingham and Ottawa follow the national policy governed by the NHSBT and the Ontario provincial policy governed by the Trillium Gift of Life Network, respectively (summarised in Supplementary Table 1).

All Nottingham patients are transplanted at Cambridge University Hospital since 2009 following a formal network arrangement; prior to this patients were transplanted at various centres through informal arrangements. Following transplantation, all patients are reviewed in a joint clinic in Nottingham, attended by teams from Cambridge and Nottingham. The care is then transferred entirely to the Nottingham team during the first 6–12 months post-transplantation. However, patients who require input from the transplant team are reviewed in the joint clinic, as needed. Similarly, Ottawa patients are primarily transplanted at Toronto General Hospital, with some transplants occurring in London (Ontario) and Montreal (Quebec), according to the preference of the patient/primary clinician. Following transplantation, patient care is transferred entirely to Ottawa during the first 3–12 months. Monthly meetings using video-conferencing is undertaken between the Ottawa team and the transplant centre where patients with transplant-related complications are discussed. Family physicians are responsible for regular monitoring of metabolic complications, and prescribe treatment based on individual care.

OUTCOMES

The primary outcome was patient survival, defined as the time from LT to death from any cause. Death-censored graft survival, development of end-stage renal disease (ESRD), major cardiovascular events (CVE), and *de novo* cancer (including non-melanoma skin cancers) were secondary endpoints. ESRD was defined as GFR <15 ml/min/1.73m2 for ≥6 months or requirement of renal replacement therapy. Myocardial infarction and stroke were considered as major CVE.

STATISTICAL ANALYSIS

Continuous variables were presented as median with interquartile range (IQR) and categorical variables were presented as number and percentage. A p-value of <0.05 was considered significant.

Kruskal-Wallis, Mann-Whitney and Chi-square test were used to compare demographics between Nottingham and Ottawa groups. Patient survival, death-censored graft survival and development of ESRD, major CVE, and *de novo* cancer were calculated using Kaplan-Meier analysis (Log-rank test).

Difference in outcomes between Nottingham and Ottawa groups was investigated using a multivariable logistic regression model, incorporating variables with a p value of <0.10 on univariate analysis. Variables were considered to have independent association only if the p-value reached Bonferroni-corrected level of significance.

All statistical analyses were performed using either GraphPad prism 8 (GraphPad, San Diego, CA) or SPSS for Windows v26 (IBM Corp, Armonk, NY, USA).

RESULTS

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

A total of 335 patients who underwent LT from Nottingham, UK (n=132) and Ottawa, Canada (n=203) were included in this study. The demographics and clinical characteristics at LT are summarised in Table 1.

Nottingham patients were younger at transplantation (median 54 [IQR 39–59] vs 56 [IQR 49–62] years, p=0.007) with lower rate of history of smoking prior to transplantation (28.8% vs 45.8%, p=0.002). Although decompensated cirrhosis was the most common indication for LT in both the Nottingham (68.2%) and Ottawa (62.6%) patient groups, ALF and HCC were the second most common indications in the Nottingham and Ottawa patient groups, respectively (ALF 24.2% Vs 5.9%, HCC 6.1% Vs 27.6%, p<0.0001). Alcohol-related liver disease was the most common aetiology of liver disease among the Nottingham patients, while hepatitis C related liver disease was the most common aetiology among the Ottawa patients (p<0.0001).

The number of patients undergoing LT has steadily increased in both centres during the study period. Majority of Nottingham patients underwent LT at the Cambridge transplant unit (n=72, 54.5%) followed by Leeds (n=32, 24.2%), Birmingham (n=21, 15.9%), King's College London (n=3, 2.3%), Newcastle (n=3, 2.3%) and Edinburgh (n=1, 0.8%). Similarly, the majority of Ottawa patients underwent LT at the Toronto transplant unit (n=140, 69.0%) followed by Montreal (n=37, 18.2%), London Ontario (n=24, 11.8%), Vancouver (n=1, 0.5%) and Halifax (n=1, 0.5%).

PATIENT SURVIVAL

Overall, 25 (18.9%) and 24 (11.8%) patients died during a median follow-up of 9.1 (IQR 4.3–15.6) and 6.5 (IQR 3.5–11.2) years in the Nottingham and Ottawa groups, respectively. The 1-, 5-, 10- and 20-year patient survival rates were 98%, 95%, 87% and 62% and 100%, 96%, 88% and 62% in the Nottingham and Ottawa groups, respectively (log-rank test p=0.87, figure 1A).

Sepsis (30.8% and 25.0%) and cancer (24.0% and 12.5%) were the most common causes of death in the Nottingham and Ottawa groups, respectively.

RECURRENCE OF PRIMARY DISEASE AND GRAFT SURVIVAL

Overall, 12 (9.1%) and 9 (4.4%) patients developed recurrence of non-viral primary disease following a median time of 11.8 (IQR 4.8 – 15.0) and 5.1 (IQR 4.4–14.3) years in the Nottingham and Ottawa groups, respectively (log-rank test p=0.68). These include 8 primary biliary cholangitis, 2 primary sclerosing cholangitis, and 2 non-alcohol fatty liver disease in Nottingham and 2 primary biliary cholangitis, 5 primary sclerosing cholangitis, 1 autoimmune hepatitis, and 1 non-alcoholic fatty liver disease in Ottawa groups. In addition, 7 of 13 (53.8%) and 46 of 71 (64.8%) patients who underwent LT for hepatitis C related liver disease were hepatitis C RNA positive at the time of transplantation. All underwent anti-viral treatment following transplantation and 5 (71.4%) and 33 (71.7%) achieved sustained virologic response (SVR). Further, alcoholic recidivism was noted in 4 of 25 (16.0%) and 4 of 31 (12.9%) patients who underwent LT for alcohol-related liver disease.

Overall, 13 (9.8%) and 7 (3.4%) patients underwent re-transplantation in the Nottingham and Ottawa groups, respectively. The most common indication for re-transplantation was hepatic artery

thrombosis (46.2%, n=6) and recurrence of primary disease (57.1%, n=4), respectively. The 1-, 5-, 10- and 20-year death-censored graft survival rates were 96%, 95%, 94% and 89%, and 99%, 98%, 98% and 96% in the Nottingham and Ottawa groups, respectively (log-rank test p=0.10, figure 1B).

END-STAGE RENAL DISEASE

A gradual decline in renal function was evident in both the Nottingham and Ottawa groups (figure 2A). Overall, 10 (7.6%) and 13 (6.4%) patients developed ESRD following a median time of 11.4 (IQR 2.0–13.2) and 9.8 (IQR 5.8–14.6) years in the Nottingham and Ottawa groups, respectively. The 1-, 5-, 10- and 20-year cumulative incidence of ESRD were 0.0%, 2.3%, 2.3% and 15.4%, and 0.5%, 1.2%, 6.7% and 26.4% in the Nottingham and Ottawa groups, respectively (log-rank test p= 0.29, figure 2B).

POST-TRANSPLANT METABOLIC SYNDROME AND MAJOR CARDIOVASCULAR EVENTS

Overall, 7 of 105 (6.7%) and 32 of 161 (19.9%) patients developed post-transplant diabetes mellitus (DM) in the Nottingham and Ottawa groups (p=0.003), respectively. Similarly, 12 of 106 (11.3%) and 65 of 159 (40.8%) developed hypertension (p<0.0001), and 3 of 120 (2.5%) and 38 of 186 (20.4%) developed dyslipidaemia (p<0.0001) following transplantation in the Nottingham and Ottawa groups, respectively. There were no significant changes in weight in both the Nottingham and Ottawa groups (figure 3A).

Overall, 4 (3.0%) and 14 (6.9%) patients developed major CVE following a median time of 7.4 (IQR 3.2–11.7) and 6.3 (IQR 4.0–11.4) years in the Nottingham and Ottawa groups, respectively. The 1-, 5-, 10- and 20-year cumulative incidence of major CVE were 0.0%, 1.0%, 1.0% and 5.4%, and 0.5%, 3.9%, 5.8% and 20.1% in the Nottingham and Ottawa groups, respectively (log-rank test p=0.008, figure 3B).

On univariate analysis, male sex (p=0.007), pre-LT DM (p=0.049), post-LT hypertension (p=0.0007), post-LT dyslipidaemia (p<0.0001) and the use of cyclosporin (p=0.002) were associated with major CVE (Table 2). In addition to the above variables and the use of tacrolimus (p=0.06) and centre (p=0.13) were included in the multivariate analysis (7 variables); the Bonferroni-corrected level of significance in the multivariate analysis was p <0.007. On multivariate analysis, development of dyslipidaemia following transplantation (OR 21.71, 95%CI 5.52–85.36; p<0.0001) was the only variable associated with the development of major CVE post-LT.

CANCER

Overall, 22 (16.7%) and 33 (16.3%) patients developed *de novo* cancer following a median time of 8.2 (IQR 4.9–13.7) and 5.9 (IQR 3.2–9.8) years in the Nottingham and Ottawa groups, respectively. The 1-, 5-, 10- and 20-year cumulative incidence of *de novo* cancer were 1.5%, 5.2%, 17.4% and 34.1%, and 1.5%, 7.5%, 19.5% and 49.9% in the Nottingham and Ottawa groups, respectively (log-rank test p= 0.22, figure 4). Skin cancer was the most common cancer in both Nottingham (22.7%) and Ottawa (42.4%) groups. This was followed by colon (13.6%) and haematological (13.6%) cancers in the Nottingham and lung (9.1%) and pancreas (9.1%) cancers in the Ottawa groups.

Two of the 9 (22.2%) and 4 of 56 (7.1%) patients who underwent LT for HCC developed recurrence of HCC following transplantation in the Nottingham and Ottawa groups, respectively (log-rank test p= 0.15). The median duration to HCC recurrence was 6.2 and 6.6 years, respectively.

DISCUSSION

This study represents the largest reported experience on the outcomes of LT recipients managed in non-transplant centres. It includes two centres; one in the UK and the other in Canada. This study reports on broader relevant post-transplant clinical outcomes (ESRD, major CVE and *de novo* cancer) in addition to conventional patient and graft survival outcomes. Despite the heterogeneities in the patient groups and policies, clinical outcomes were similar in Nottingham and Ottawa.

The 1- and 5-year patient survival, according to the 2017/2018 annual report published by the NHSBT, which includes 8428 liver transplants recipients, were 90-94% and 80-81%, respectively [https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12250/nhsbt-liver-transplantation-annual-report-2017-2018.pdf]. Similarly, the 1-, 3- and 5-year survival rates, according to the 2012 annual report published by the Canadian Organ Replacement Register, which includes 5654 liver transplants recipients, were 92%, 82-88% and 78-83%, respectively [https://secure.cihi.ca/free_products/2014_CORR_Annual_Report_EN.pdf]. Interestingly, the survival rates of patients followed up in Nottingham and Ottawa were numerically better than their respective national rates. Although exploring the reasons behind such difference is beyond the scope of this study, it would not be unreasonable to speculate that it may likely be due to the relatively smaller study cohort and the potential for a risk-averse approach to patient selection in non-transplant centres. In addition, 'sicker' patients are likely to be kept within the liver transplant centre programme for follow-up; however, this reflects accepted clinical practice and is not necessarily a weakness of our study. Rather, this lends additional evidence that the majority of patients who undergo uneventful liver transplantation can be safely followed outside liver transplant centres.

The recurrence of autoimmune liver diseases following LT ranges from 10 to 50% [7-9]. In line with the previous literature, the recurrence rates of autoimmune liver diseases in our cohorts were 25% (10 out of 40) and 21% (8 out of 39) in Nottingham and Ottawa, respectively. However, it is important to note that conforming to the national practices neither Nottingham nor Ottawa undertake routine screening for recurrence with protocol liver biopsy or surveillance imaging. In our study, the overall post-LT hepatitis C SVR rates were just over 70% in both centres. Although the SVR rates are markedly lower than the direct-acting antiviral (DAA) SVR rates, it is important to highlight that a substantial period of our study predates DAA treatment. However, the overall re-transplantation rates of our study were also comparable to that of previous literature from both Europe and North America [10-12].

ESRD, major CVE and *de novo* cancer are being increasingly used in the literature along with the patient and graft survival rates in reporting outcomes following organ transplantation both in adult and paediatric population [13-15]. Our findings are on par with a recent study that reported rates of ESRD and major CVE of 9% and 5%, respectively [12], and our study findings are on par with this. However, the development of *de novo* malignancy rates was higher in both our centres compared to previously reported rates of 5.6% – 8.7% [12, 16, 17]. We speculate that our relatively smaller study cohort and the potential for missing data in large database studies may have contributed the above differences.

Although the indications for LT, namely decompensated cirrhosis, HCC and ALF, are broadly similar, Nottingham and Ottawa follow different listing polices. For example, while a modified Milan criteria

is used in the UK, Total Tumour Volume/alpha-fetoprotein criteria is used in Ontario for the selection of patients with HCC. Further, the allocation of donor organ policies also differ between Nottingham and Ottawa. In addition, there were intrinsic differences between the Nottingham and Ottawa cohorts (Table 1). The Nottingham cohort was relatively younger with significantly higher proportion of patients with ALF, likely due to paracetamol-related ALF being more common in the UK [18-21]. Further, due to the geography, the distance and travel time to transplant centres are substantially higher in Canada than in the UK. However, the above-mentioned differences, did not impact the overall long-term outcomes of LT recipients in Nottingham and Ottawa, which is encouraging.

Our data combined with excellent patient and graft survival outcome results from other non-transplant centres within UK [22, 23], promises a way forward for delivering pre- and post-transplant patient care close to home without compromising patient wellbeing. Video-conferencing technology has already been successfully used to increase access to care in underserved areas in Canada, most notably in the treatment of hepatitis C infection and is increasingly used in the management of transplant recipients in non-transplant centres. Further, outreach clinics are becoming part of day-to-day clinical service provision. Trainees are also being exposed to transplant hepatology as part of their regular training [24, 25] and majority of them continue their career in non-transplant centres, a resource that could be optimally exploited in providing patient care close to home. These would likely mitigate the barriers to transplant service [26], while helping to reduce the clinical burden on transplant centres. It would also improve access to healthcare and equalise service provision nationally. All of this would help to remove some of the patient care burden from transplant centres and allow transplant services to grow beyond their geographical limits [27]. Further, this may improve organ donation rates from regions away from transplant centres as people see more visible "benefit" to the local population, and thereby overcome the societal behaviours and beliefs that currently create barriers to donation [28]. Cost analysis, based on NHS reimbursement tariff per transplant, show financial sustainability of providing post-transplant service in non-transplant centres such as Nottingham (MWJ, personal communication).

Our study has certain strengths and limitations. It is the largest study of its kind and it reports on both conventional and broader relevant clinical outcomes of LT recipients. Our study compares two centres in two different jurisdictions with different transplant polices, protocols and patient populations. This study reports on outcomes over a long period, during which surgical techniques, pre- and post-transplant care and use of immunosuppression have undergone changes, as in any other field of medicine, and is unavoidable. Although the differences in patient populations and significant changes in patient care may have impacted the study results, demonstration of comparable outcomes despite these unavoidable differences is a major strength of this study. On the other hand, the retrospective nature of our study is a natural limitation, due to the risk of bias inherent to study design and the unavailability of data for some variables, such as donor characteristics and intra-operative factors that may have impacted the outcomes. Further, the differences in post-transplant outcomes between centres could not be investigated adequately due to lack of data on all potential risk factors that may have contributed to these differences (e.g. maintenance immunosuppression dose, protocols for the use of statins and anti-hypertensives, etc.). Implementation of similar transplant service provision models will depend on individual healthcare systems and the availability of clinicians trained in transplant medicine, and it would be wrong to assume that similar service provision could be adopted in other countries.

In conclusion, this is the largest non-registry study to investigate outcomes of LT recipients managed at non-transplant centres. It clearly demonstrates that satisfactory long-term outcomes comparable to that of national and international outcomes are achievable in non-transplant centres, despite the differences in transplant policies, protocols and healthcare systems. This study provides promising preliminary data to build towards future changes to public healthcare policy; namely, additional resources to increase local care for post-transplant patients, while increasing access to subspecialists via virtual care. This is particularly important in the era of COVID-19, when travel and in-person healthcare visits are discouraged. Future studies should aim to provide prospective comparisons of different models of post-LT care and include additional 'non-traditional' outcomes such as cost-effectiveness and patient satisfaction, which would greatly assist in effecting these policy changes.

FIGURE LEGENDS

FIGURE 1

Kaplan-Meier estimates of patient survival (A) and death-censored graft survival (B) following liver transplantation of patients followed up in Nottingham, UK (blue) and Ottawa, Canada (green).

FIGURE 2

Comparison of estimated glomerular filtration rate levels (A) and Kaplan-Meier estimates of the development of end-stage renal disease (B) of patients followed up in Nottingham, UK (blue) and Ottawa, Canada (green).

FIGURE 3

Comparison of weight (A) and Kaplan-Meier estimates of the development of major cardiovascular events (B) of patients followed up in Nottingham, UK (blue) and Ottawa, Canada (green).

FIGURE 4

Kaplan-Meier estimates of the development of de novo cancer of patients followed up in Nottingham, UK (blue) and Ottawa, Canada (green).

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TABLES

Table 1: Demographics and clinical characteristics of Nottingham and Ottawa patients included in the study

		All (n=335) median (IQR) or number (%)	Nottingham (n=132) median (IQR) or number (%)	Ottawa (n=203) median (IQR) or number (%)	p value
Age at LT (years)		55 (46 – 61)	54 (39 – 59)	56 (49 – 62)	**0.007**
Female sex		118 (35.2%)	51 (38.6%)	67 (33.0%)	0.29
Pre-LT	**DM**	69 (20.6%)	27 (20.5%)	42 (20.7%)	0.96
	Hypertension	70 (20.9%)	26 (19.7%)	44 (21.7%)	0.66
	Dyslipidaemia	29 (8.7%)	12 (9.1%)	17 (8.4%)	0.82
	CVD	12 (3.6%)	3 (2.3%)	9 (4.4%)	0.30
	Malignancy†	22 (6.6%)	3 (2.3%)	7 (3.4%)	0.54
History of Pre-LT Smoking		131 (39.1%)	38 (28.8%)	93 (45.8%)	**0.002**
Aetiology	**ALD**	56 (16.7%)	25 (18.9%)	31 (15.3%)	**<0.0001**
	NAFLD	29 (8.7%)	9 (6.8%)	20 (9.9%)	
	HCV	84 (25.1%)	13 (9.8%)	71 (35.0%)	
	HBV	16 (4.8%)	4 (3.0%)	12 (5.9%)	
	AIH	15 (4.5%)	5 (3.8%)	10 (4.9%)	
	PBC	31 (9.3%)	18 (13.6%)	13 (6.4%)	
	PSC	33 (9.9%)	17 (12.9%)	16 (7.9%)	
	Others	71 (21.2%)	41 (31.1%)	30 (14.8%)	
Indication	**ALF**	44 (13.1%)	32 (24.2%)	12 (5.9%)	**<0.0001**
	Decompensation	217 (64.8%)	90 (68.2%)	127 (62.6%)	
	HCC	64 (19.1%)	8 (6.1%)	56 (27.6%)	
	Other	10 (3.0%)	2 (1.5%)	8 (3.9%)	
LT Decade	**1987 – 1996**	22 (6.6%)	12 (9.1%)	10 (4.9%)	**0.007**
	1997 – 2006	92 (27.5%)	46 (34.8%)	46 (22.7%)	
	2007 – 2016	221 (66.6%)	74 (56.1%)	147 (72.4%)	
Peri-LT RRT		9 (2.7%)	0 (0.0%)	9 (4.4%)	na
Donor type	**DBD**	274 (81.8%)	117 (88.6%)	157 (77.3%)	**<0.0001**
	DCD	16 (4.8%)	14 (10.6%)	2 (1.0%)	
	LD	45 (13.4%)	1 (0.8%)	44 (21.7%)	

A p value <0.05 in indicated in bold. †History of non-hepatocellular carcinoma malignancies prior to transplantation.
Abbreviations: AIH autoimmune hepatitis; ALD alcohol-related liver disease; ALF acute liver failure; CVD cardiovascular disease; DBD donation after brainstem death; DCD donation after circulatory death; DM diabetes mellitus; HBV hepatitis B; HCC hepatocellular carcinoma; HCV hepatitis C; LD living donor; LT liver transplantation; NAFLD non-alcoholic fatty liver disease; PBC primary biliary cholangitis; PSC primary sclerosing cholangitis.

Table 2: Predictors of major cardiovascular events – univariate and multivariate logistic regression

	Univariate analysis	Multivariate analysis	
	p value	OR (95% CI)	p value
Age at listing	0.18		
Male sex*	0.007	9.98 (1.20 – 82.92)	0.03
BMI at first year of transplantation	0.20		
Aetiology of liver disease	0.34		
Pre-transplant DM*	0.049	3.11 (0.92 – 10.57)	0.07
Pre-transplant hypertension	0.46		
Pre-transplant dyslipidaemia	0.63		
Pre-transplant CVE	0.71		
History of smoking	0.33		
Post-transplant DM	0.15		
Post-transplant hypertension*	0.0007	1.47 (0.42 – 5.16)	0.55
Post-transplant dyslipidaemia*	<0.0001	21.71 (5.52 – 85.36)	**<0.0001**
Use of Tacrolimus*	0.07	1.28 (0.21 – 7.77)	0.79
Use of Cyclosporin*	0.002	6.37 (0.94 – 43.33)	0.06
Use of Sirolimus	0.53		
Centre (Nottingham/Ottawa)†	0.13	0.53 (0.12 – 2.31)	0.40

Parameters with a p-value <0.10 on univariate analysis were included in the multivariate analysis and these parameters are indicated by an asterisk (*). †Variable 'centre' was forced included in the multivariate analysis. The Bonferroni-corrected level of significance in this analysis was **p <0.007 and is indicated in bold**.
Abbreviations: BMI body mass index; CVE cardiovascular event; DM diabetes mellitus.

Supplementary Table 1: Summary of selection criteria for first adult liver transplantation in the UK and Ontario, Canada

Indication	UK Criteria	Ontario, Canada Criteria
ALF	• Paracetamol poisoning - pH <7.25 24 hours after overdose and after fluid resuscitation - PT >100s (INR >6.5) and creatinine >300μmol/l or anuria and grade 3–4 encephalopathy - arterial lactate >5 mmol/l on admission and >4 mmol/l 24 hours after and clinical encephalopathy - deterioration (e.g. ↑ICP, FiO_2 >50%, ↑inotrope requirements) and 2 of the following 3: PT >100s (INR >6.5), serum creatinine >300μmol/l or anuria, or grade 3–4 encephalopathy • Non-paracetamol aetiologies: clinical encephalopathy and - PT >100 (INR >6.5) or - three of the following: age >40 years, PT >50s (INR >3.5), jaundice to encephalopathy time >7 days or bilirubin >300μmol/l • Wilson's disease: coagulopathy and encephalopathy • Budd-Chiari syndrome: coagulopathy and encephalopathy	• King's College Criteria or other validated criteria
Decompensated CLD	Any aetiology with a UKELD score ≥49	Any aetiology with a Na-MELD score ≥15
HCC	• Single tumour ≤5cm • Up to 5 tumours all ≤3cm • Single tumour >5cm and ≤7cm with no evidence of tumour progression over a 6-month period with or without locoregional therapy (AFP ≤1,000IU/ml, tumour rupture, extra-hepatic spread and macroscopic vascular invasion are absolute contraindications)	• TTV ≤145cm^3 and AFP ≤1,000 IU/ml (extra-hepatic spread, vascular invasion and HCC mixed with predominance of cholangiocarcinoma are absolute contraindications)
Other	• Variant syndrome with a UKELD score <49 - diuretic resistant ascites - chronic hepatic encephalopathy - intractable pruritus - hepatopulmonary syndrome - recurrent cholangitis - polycystic liver disease - familial amyloid polyneuropathy - familial hypercholesterolaemia - hepatic epithelioid haemangioendothelioma	• Na-MELD score 11 – 14 and deemed to have poor prognosis that is not captured by the MELD score (e.g. recurrent cholangitis, refractory ascites) • Complications of end-stage liver disease or portal hypertension (e.g. hepatopulmonary syndrome) • Metabolic disorders (e.g. Hereditary Transthyretin Amyloidosis, Maple Syrup Urine Disease and Hyperoxaluria type I) • Selected cholangiocarcinoma (within the Mayo Clinic protocol) • Selected neuroendocrine liver tumours • Selected hepatoblastomas

Abbreviations: AFP α-fetoprotein; ALF acute liver failure; CLD chronic liver disease; FiO_2 fraction of inspired oxygen; HCC hepatocellular carcinoma; ICP intracranial pressure; INR international normalised ratio; Na-MELD sodium model for end-stage liver disease score; PT prothrombin time; TTV total tumour volume; UKELD United Kingdom end-stage liver disease score.