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AIM AND SCOPE

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WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Retrospective Cohort Study

Impact of comorbidity on waiting list and post-transplant outcomes in patients undergoing liver retransplantation

Mohammad A B Al-Freah, Carl Moran, Matthew R Foxton, Kosh Agarwal, Julia A Wendon, Nigel D Heaton, Michael A Heneghan

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Abstract**AIM**

To determine the impact of Charlson comorbidity index (CCI) on waiting list (WL) and post liver retransplantation (LRT) survival.

METHODS

Comparative study of all adult patients assessed for primary liver transplant (PLT) ($n = 1090$) and patients assessed for LRT ($n = 150$), 2000-2007 at our centre. Demographic, clinical and laboratory variables were recorded.

RESULTS

Median age for all patients was 53 years and 66% were men. Median model for end stage liver disease (MELD) score was 15. Median follow-up was 7-years. For retransplant patients, 84 (56%) had ≥ 1 comorbidity. The most common comorbidity was renal impairment in 66 (44.3%). WL mortality was higher in patients with ≥ 1 comorbidity (76% vs 53%, $P = 0.044$). CCI (OR = 2.688, 95%CI: 1.222-5.912, $P = 0.014$) was independently associated with WL mortality. Patients with MELD score ≥ 18 had inferior WL survival (Log-Rank 6.469, $P = 0.011$). On multivariate analysis,

CCI (OR = 2.823, 95%CI: 1.563-5.101, $P = 0.001$), MELD score ≥ 18 (OR 2.506, 95%CI: 1.044-6.018, $P = 0.04$), and requirement for organ support prior to LRT ($P < 0.05$) were associated with reduced post-LRT survival. Donor/graft parameters were not associated with survival ($P = NS$). Post-LRT mortality progressively increased according to the number of transplanted grafts (Log-Rank 18.455, $P < 0.001$). Post-LRT patient survival at 1-, 3- and 5-years were significantly inferior to those of PLT at 88% *vs* 73%, $P < 0.001$, 81% *vs* 71%, $P = 0.018$ and 69% *vs* 55%, $P = 0.006$, respectively.

CONCLUSION

Comorbidity increases WL and post-LRT mortality. Patients with MELD ≥ 18 have increased WL mortality. Patients with comorbidity or MELD ≥ 18 may benefit from earlier LRT. LRT for ≥ 3 grafts may not represent appropriate use of donated grafts.

Key words: Hepatic; Organ; Outcome; Diabetes; Renal

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Core tip: The prevalence and impact of comorbidity on waiting list (WL) and post-transplant survival is unknown in patients who had liver retransplantation. This study identified comorbidity(ies) were common (56%) in this cohort, most with renal impairment. WL mortality was higher in patients with ≥ 1 comorbidity and model for end stage liver disease (MELD) score ≥ 18 . Post-transplant survival was inferior in patients with ≥ 1 comorbidity, MELD score ≥ 18 and in patients who required organ support prior to retransplantation. Comorbidity increases WL and post-transplant mortality. Patients with comorbidity or MELD ≥ 18 may benefit from earlier retransplantation.

Al-Freah MAB, Moran C, Foxton MR, Agarwal K, Wendon JA, Heaton ND, Heneghan MA. Impact of comorbidity on waiting list and post-transplant outcomes in patients undergoing liver retransplantation. *World J Hepatol* 2017; 9(20): 884-895 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i20/884.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i20.884>

INTRODUCTION

Liver retransplantation (LRT) represents the only viable option for survival for some patients who develop graft failure following primary liver transplant (PLT). Published reports on cohorts of patients who underwent LRT indicate inferior post-transplant survival in these patients^[1-5]. There has been an increase in the number of patients awaiting PLT which was not associated with increase in donated organs^[6]. Although transplant programmes have tried to compensate for this increase in demand by more liberal use of marginal grafts,

there is evidence that death on the waiting list (WL) for patients listed for PLT remains high^[7]. Therefore, the combination of increased WL mortality with increasing demand for PLT coupled with the known inferior outcomes of LRT; raises concerns and generates ethical debate in the transplant community on the use of scarce resource of donated organs for LRT^[8].

This debate has motivated researchers to identify predictors of survival following LRT to improve the selection of patients who might benefit most from LRT. Model for end-stage liver disease (MELD) score > 25 , recipient age, creatinine level, bilirubin level, indication for retransplantation, the urgency for LRT, coma episodes, haemoglobin (Hb) level and the number of fresh frozen plasma units transfused were identified as factors associated with reduced post-LRT survival in a number of studies^[3,5,9,10]. Death or graft loss was shown to increase gradually following LRT according to the timing of LRT with marked increase in risk between 4-38 d following LRT^[11-13]. Inferior survival was also observed according to increasing number of transplanted graft^[13].

Comorbidity as defined by the Charlson comorbidity index (CCI) was found to adversely affect post-transplant survival in patients who underwent PLT^[14]. Thuluvath *et al*^[7] analysed the data of the scientific registry of transplant recipients (SRTR) in the United States from 1999 to 2008. The prevalence of comorbidity such as diabetes mellitus (DM), renal impairment (RI) and obesity was found to have steadily increased in candidates listed for liver transplantation over the ten year period^[7]. However, the prevalence and impact of comorbidity on WL and post-transplant survival in patients listed for LRT have not been studied previously.

The aims of this study were three fold, firstly, to identify the prevalence of comorbidity according to CCI in patients listed for LRT, secondly, to study the impact of comorbidity on WL and post-LRT mortality, and finally, to identify other factors associated with reduced WL and post-LRT survival.

MATERIALS AND METHODS

Patients and design

This is a retrospective study of all patients referred to the liver unit at King's for LRT assessment between January 2000 and December 2007. There were 151 assessments for LRT on 137 patients over the 8 year period. One patient was excluded because of incomplete information. Data analysis was performed on 150 LRT assessments. We utilized a cohort of patients who underwent PLT over the same time period for comparison of outcomes of PLT and LRT ($n = 1332$). Patients assessed for acute liver failure ($n = 175$), familial amyloid polyneuropathy (43) and 24 with incomplete information were excluded. We analysed data on 1090 patients with end stage liver disease (ESLD) who were assessed for PLT.

Data

All patients assessed for liver transplantation at our centre had their clinical, laboratory, radiological and histological data as well as the outcome of transplant assessment entered at the time of liver transplant assessment into a prospective electronic database. This database was analysed in addition to electronic patient records and clinical notes to record demographic, clinical and laboratory variables of this cohort. Prognostic scores such as MELD and United Kingdom model for end-stage liver disease (UKELD) scores were calculated at the time of assessment and at the time of transplantation. MELD was calculated according to the UNOS adjustment^[15]. The UKELD score was calculated according to Barber *et al.*^[16]. Donor and graft variables were collected and donor risk index was calculated according to Feng *et al.*^[17]. Patient survival was recorded according to their survival status in our hospital information system and further confirmed using the National Health System electronic portal. This is a United Kingdom wide national database, where patient survival status is updated according to the generation of death certificates in the United Kingdom.

Definitions of outcome measures

WL outcome was defined for this study by death on WL or delisting because of significant deterioration or hepatocellular carcinoma (HCC) progression beyond Milan criteria whilst awaiting LT. To study the influence of comorbidity and other variables on listing outcome, we used the transplant free survival (defined as time from listing to death, time to delisting or time to transplant) to eliminate the artificial impact of transplantation on survival of this cohort. Post-transplant patient survival was defined as time from transplantation to death, and if alive, censored on 01/11/2011. Graft survival was defined as time from transplantation to retransplantation or death, and if alive censored on 01/11/2011. Patients who were lost to follow-up were censored as being alive at the date of their last follow-up. Post-LRT patient survival was defined as time from second or subsequent transplant to death, and if alive, censored on 01/11/2011. Post-LRT graft survival was defined as time from second or subsequent transplant to further retransplantation or death, and if alive censored on 01/11/2011. One-year post transplant patient survival was defined as time from LRT to death, and if alive, censored at 12 mo following transplantation. One-year post transplant graft survival was defined as time from transplantation to retransplantation or death, and if alive censored at 12 mo following transplantation. Marginal grafts were defined as graft with Donor Risk Index > 1.8^[7]. Cut off values for MELD score of 18 and 25 were chosen according to Rosen *et al.*^[18] and Edwards and Harper^[19].

Comorbidities

Nine comorbidities were prospectively defined according

to Volk *et al.*^[14]. These included congestive heart failure, coronary artery disease, DM, peripheral vascular disease, cerebro-vascular disease, chronic pulmonary disease, connective tissue disease, RI and malignancy. DM was defined as a chronic hyperglycaemia requiring medication use at any time during the month preceding transplant assessment. RI was defined as serum creatinine of ≥ 1.5 mg/dL (≥ 132 μ mol/L) on transplant assessment, being on renal replacement therapy or history of renal transplantation. Congestive heart failure was defined as documented decrease in left ventricular function on echocardiogram or left ventricle angiogram; or increased pulmonary artery pressure of ≥ 25 mmHg on echocardiogram or on invasive pulmonary artery pressure study, including patients with porto-pulmonary hypertension. Coronary artery disease was defined as documented history of myocardial infarction or abnormal coronary angiography. All patients underwent a functional cardiac assessment of ischemia either with Bruce protocol exercise tolerance test or cardio-pulmonary exercise test. Those with positive functional test but negative coronary angiogram were not considered as having coronary artery disease. Peripheral vascular disease was defined as documented history of peripheral ischaemia on angiography, abnormal ankle-brachial index or history of vascular bypass surgery. Cerebrovascular disease was defined as a history of stroke with residual neurological deficit. Chronic pulmonary disease was defined as chronic pulmonary disease requiring medication, a forced expiratory volume of < 1.5 L or history of intubation for respiratory failure. Connective tissue disease was defined as a rheumatologist diagnosis of rheumatoid arthritis, systemic lupus erythematosus, scleroderma or spondyloarthropathies excluding patients with arthralgia without evidence of inflammatory arthritis or those with osteoarthritis. Malignancy was defined as documented history of any malignancy excluding HCC or non melanoma skin cancers. To calculate the CCI, each comorbidity was assigned 1 point when present and was assigned 0 points when absent. The CCI was calculated as the sum of points of all 9 comorbidities. CCI was calculated at the time of assessment and at the time of transplantation.

Statistical analysis

Continuous variables were presented as median (range) and analysed using non-parametric methods (Mann Whitney-*U* or Kruskal Wallis test) for non-normally distributed data as appropriate. Categorical variables were presented as numbers (percentages) and analysed using χ^2 test or Fisher's exact test as appropriate. Cox proportional hazard analysis was used to identify factors associated with listing and transplant outcomes. Factors associated with outcome (*P*-value < 0.05) were entered into multivariate analysis. Collinearity diagnostics were used to determine whether variables

Table 1 Baseline characteristics for patients who had primary liver transplantation and those who had liver retransplantation

Variables	PLT (n = 1090)	LRT (n = 150)	P value
Demographic			
Age	54 (18-82)	46 (18-72)	< 0.001
Gender (male, %)	736 (67.5)	80 (53.3)	0.001
Etiology			
ALD (%)	345 (31.7)	18 (12.0)	< 0.001
Viral (%)	303 (27.8)	50 (33.3)	0.159
Cholestatic and autoimmune (%)	227 (20.8)	34 (22.7)	0.604
Clinical			
Na, mmol/L	135 (116-151)	138 (118-150)	< 0.001
Creatinine, mg/dL	1.0 (0.4-6.8)	1.3 (0.7-8.3)	< 0.001
Bilirubin, mg/dL	2.7 (0.2-68.4)	4.7 (0.4-56.3)	< 0.001
INR	1.3 (0.8-5.0)	1.2 (0.8-13.0)	0.078
MELD	14 (6-40)	20 (6-40)	< 0.001
UKELD	55 (43-77)	56 (44-79)	0.041
Ascites (%)	669 (62.9)	38 (25.5)	< 0.001
Encephalopathy (%)	350 (33.0)	52 (34.9)	0.637

ALD: Alcohol-related liver disease; INR: International normalised ratio; MELD: Model for end-stage liver disease; UKELD: United Kingdom end-stage liver disease model; PLT: Primary liver transplantation; LRT: Liver retransplantation.

entered into a model were collinear. MELD, UKELD, Child-Turcotte-Pugh (CTP), renal impairment and sodium level showed high collinearity (variance inflation factor - VIF > 5). Once MELD and UKELD were removed of the model, CTP, sodium level and renal impairment and all other individual comorbidities showed no collinearity (VIF < 3). Kaplan-Meier analysis was performed to assess survival outcomes. Statistical analyses were performed with SPSS software (SPSS® 17.0 for Windows® SPSS Inc, Chicago, IL, United States).

RESULTS

Patient characteristics

One hundred and fifty assessments for LRT were examined and compared to a control group of 1090 patients assessed for PLT. Median follow-up was 7 years (3-12). There were 124 assessments for a second transplant, 21 assessments for a third transplant, 3 assessments for a fourth transplant, and 1 assessment each for a fifth and sixth transplant out of 150 LRT assessments. Out of these 150 assessments for LRT, six were not listed for LRT (two because of early referral, 1 because of alcohol abuse, 1 declined re-listing, 1 with complete porto-mesenteric thrombosis and 1 died during the assessment process. Only 121 patients received LRT of the 144 listed patients. Twenty three patients were delisted for the following reasons: 12 died awaiting a graft, 6 had significant clinical improvement and 5 were delisted because of significant clinical deterioration, whilst on WL. Information regarding mechanical ventilation, renal replacement therapy, vasopressor support and location of patient [home, hospital or intensive care unit (ICU)] prior to LRT was available on 113 patients. Thirty two patients (28%) received renal replacement therapy, 21 (19%) received mechanical ventilation and 20 (18%) received vasopressor support prior to LRT. Forty four patients

(36%) were transplanted from the hospital ward, 40 (33%) were transplanted from ICU and 28 (23%) were transplanted from home.

Table 1 summarises baseline characteristics according to PLT and LRT. LRT patients were significantly younger and were less likely to have ascites. However, this group were more likely to have higher median serum sodium levels (Na), creatinine values, bilirubin levels, MELD and UKELD scores ($P < 0.05$). There were no significant differences in proportion of patients with encephalopathy or median INR level between groups ($P = NS$).

Indications for LRT

The most common indication for LRT was vascular complications (thrombotic and non-thrombotic infarction of the graft) in 49 (33%) followed by graft rejection in 40 (27%), disease recurrence in 35 (23%), early graft dysfunction in 18 (12%) and 8 for other indications (5%). There were 30 patients (20%) who had biliary complications; however, only 3 (10%) patients developed graft failure secondary to biliary complications. Biliary strictures following PLT (anastomotic, hilar, papillary stenosis) were managed endoscopically, except for 2 patients who required per cutaneous biliary interventions. Eventually, 8 patients (27%) underwent biliary reconstruction for definitive management of post-transplant biliary complications. Thirty seven (78%) of patients with vascular-related complications had hepatic artery thrombosis, 9 (18%) had non thrombotic graft infarction, 1 (2%) had veno-occlusive disease and 1 (2%) had portal vein thrombosis resulting in graft infarction.

Comorbidities

There were 84 patients (56%) who had ≥ 1 comorbidity as defined by CCI. The most common comorbidity was RI in 66 (44.3%), followed by DM in 25 (16.8),

Table 2 Factors associated with waiting list mortality in liver retransplantation patients on univariate and multivariate Cox proportional hazard analysis

Variable	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age > 60 yr	2.959	0.550-3.896	0.048	3.102	1.015-9.484	0.047
DM	1.587	0.499-5.042	0.434			
Renal impairment	4.771	1.496-15.217	0.008	3.802	1.147-12.603	0.029
CCI continuous	3.121	1.589-6.130	0.001	2.688	1.222-5.912	0.014
CCI dichotomous	6.528	1.472-28.962	0.014	5.475	1.177-25.646	0.030
Hb, g/dL	0.755	0.545-1.047	0.092			
Platelet count, $\times 10^9$ /mL	0.994	0.986-1.001	0.090			
Bilirubin, mg/dL	1.012	0.979-1.045	0.481			
Creatinine, mg/dL	3.200	1.888-5.421	< 0.001	2.691	1.261-5.740	0.010
INR	1.489	1.055-2.102	0.024	1.406	0.967-2.044	0.075
Encephalopathy	2.049	0.620-6.770	0.239			
Ascites	2.781	1.006-7.682	0.049			
MELD	1.154	1.067-1.248	< 0.001	2.691	1.261-5.740	0.01
MELD \geq 18	3.827	1.190-12.315	0.024	4.369	1.255-15.215	0.021
Na, mmol/L	0.945	0.870-1.027	0.180			
UKELD	1.121	1.029-1.220	0.009	1.117	1.037-1.204	0.003

DM: Diabetes mellitus; CCI: Charlson comorbidity index; Hb: Haemoglobin; INR: International normalised ratio; MELD: Model for end-stage liver disease; Na: Serum sodium; UKELD: United Kingdom end-stage liver disease model.

chronic pulmonary disease in 2 (1.3%) and 1 patient (0.7%) for each of cerebrovascular disease, connective tissue disease and history of previous malignancy. None of the patients had coronary artery disease, congestive heart failure or peripheral vascular disease according to CCI definitions. There was higher percentage of patients who died on the WL or delisted with ≥ 1 comorbidity compared to those without any comorbidity (76% vs 53%, $P = 0.044$). There was a higher percentage of patients with ≥ 1 comorbidity in those assessed for LRT compared to those assessed for PLT (56% vs 43%, $P = 0.002$). The CCI (HR = 2.688, 95%CI: 1.222-5.912, $P = 0.014$) and the presence of any comorbidity (HR = 5.475, 95%CI: 1.177-25.646, $P = 0.030$) were independently associated with WL mortality on Cox proportional hazard analysis (Table 2). Only DM and RI as individual comorbidities were included in the Cox model because of the infrequency of other comorbidities in this cohort. RI (HR = 3.802, 95%CI: 1.147-12.603, $P = 0.029$) was independently associated with WL mortality. WL mortality in patients with any comorbidity was higher compared to those without comorbidities as shown in Figure 1.

With regards to post-transplant outcomes, the CCI (HR = 2.823, 95%CI: 1.563-5.101, $P = 0.001$) and the presence of comorbidity (HR = 2.870, 95%CI: 1.306-6.307, $P = 0.009$) were independently associated with 12-mo patient and graft survival post-LRT on Cox proportional hazard analysis (Table 3).

WL mortality

Sixteen out of 144 patients (11%) died awaiting a graft. Eight had disease recurrence (of which 5 had HCV recurrence), 3 had vascular complications, 4 had graft rejection and 1 had other indication for LRT. None of the patients with early graft dysfunction died

awaiting a graft. WL mortality for PLT was significantly higher compared to LRT (24% vs 11%, $P < 0.001$). However, median waiting time was significantly shorter for LRT compared to PLT (16 d, range: 0-1118 d vs 100 d, range: 1-922, $P < 0.001$).

Table 2 summarises variables associated with WL mortality on univariate and multivariate analysis. Only age > 60 years and the presence of ascites were included as fixed variables in the multivariate model to prevent interaction of variables with similar clinical relevance (such as creatinine, MELD, RI, comorbidity). Factors which were independently associated with WL mortality were age > 60 years, RI, creatinine level, the presence of comorbidity, CCI, MELD score and UKELD score. Figure 2 illustrates significantly increased 12 mo WL mortality in patients with MELD score ≥ 18 on Kaplan Meier survival analysis (Log-Rank: 6.741, $P = 0.009$). Similar findings observed with MELD cut-off value of 25 (Log-Rank: 8.195, $P = 0.004$). WL mortality was not increased when comparing patients listed for their second graft ($n = 118$) to those listed for their third or more grafts ($n = 26$) (Log-Rank: 0.156, $P = 0.693$).

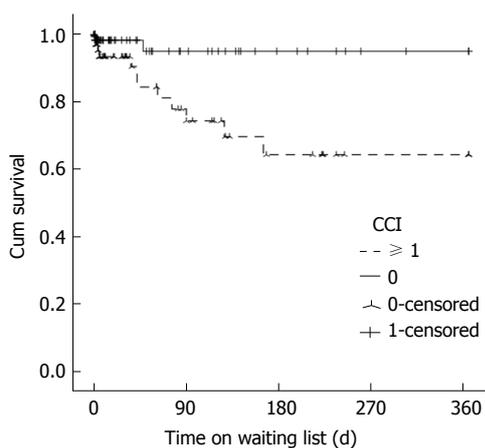
Post-transplant outcomes

The 1-, 3- and 5-year post-transplant patient and graft survival were significantly lower for patients who had LRT compared to those who had PLT. Figure 3 summarise these findings. In retransplanted patients, patient and graft survival were significantly different according to the number of grafts transplanted as analysed by Kaplan Meier survival method (Figure 4). The difference is mainly attributed to the inferior post-transplant survival of patients who had ≥ 3 transplants. There was no significant difference in patient or graft survival between patients who had

Table 3 Univariate and multivariate analysis of factors associated with 1-year post-transplant patient and graft survival of retransplanted patients on Cox proportional hazard analysis

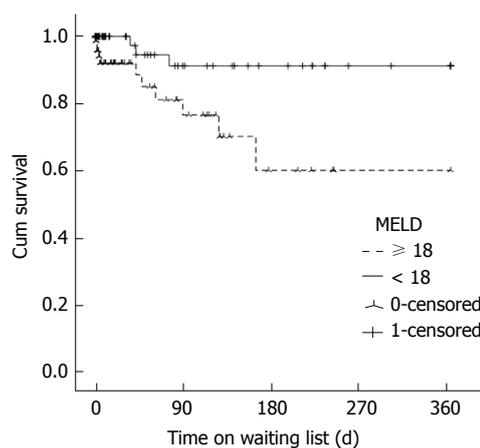
Variable	Patient survival			Graft survival		
	HR	95%CI	P value	HR	95%CI	P value
Univariate analysis						
Age	0.796	0.973-1.021	0.997	0.992	0.969-1.016	0.515
Early graft dysfunction	2.143	0.919-4.998	0.078	1.788	0.776-4.123	0.173
DM	2.242	0.961-5.228	0.062	2.004	0.869-4.618	0.103
Renal impairment	4.385	2.133-9.017	< 0.001	3.494	1.759-6.941	< 0.001
CCI continuous	3.344	1.949-5.738	< 0.001	2.755	1.638-4.633	< 0.001
CCI dichotomous	3.56	1.691-7.493	0.001	2.751	1.377-5.494	0.004
Pre-LRT mechanical ventilation	3.044	1.461-6.342	0.003	2.456	1.210-4.983	0.013
Pre-LRT vasopressor support	4.714	2.239-9.928	< 0.001	3.618	1.758-7.443	< 0.001
Pre-LRT renal replacement therapy	4.233	2.029-8.829	< 0.001	3.271	1.630-6.562	0.001
Transplant from ICU	2.744	1.318-5.712	0.007	2.101	1.049-4.206	0.036
MELD score ≥ 18	4.714	2.239-9.928	0.009	3.105	1.399-6.890	0.005
Encephalopathy at LRT	2.593	1.213-5.544	0.014	2.28	1.121-4.639	0.023
Hb, g/dL	0.791	0.629-0.994	0.044	0.792	0.636-0.985	0.037
ABO mismatch	2.37	1.015-5.532	0.046	2.338	1.053-5.190	0.037
Cold ischemia time (h)	1.113	0.987-1.255	0.082	1.081	0.962-1.216	0.191
DRI	0.68	0.236-1.963	0.476	0.693	0.250-1.918	0.476
DRI > 1.8	1.736	0.772-3.902	0.180	1.67	0.747-3.737	0.212
Multivariate analysis						
Renal impairment	3.215	1.147-12.603	0.005	2.543	1.160-5.573	0.020
CCI Continuous	2.823	1.563-5.101	0.001	2.350	1.331-4.148	0.003
CCI Dichotomous	2.87	1.306-6.307	0.009	2.223	1.067-4.633	0.033
Pre-LRT mechanical ventilation	2.52	1.126-5.637	0.024	2.099	0.968-4.552	0.060
Pre-LRT vasopressor support	4.004	1.554-10.314	0.004	3.023	1.216-7.514	0.017
Pre-LRT renal replacement therapy	2.691	1.261-5.740	0.01	2.441	1.107-5.383	0.027
Transplant from ICU	1.859	0.794-4.354	0.153	1.437	0.640-3.230	0.380
MELD score ≥ 18	2.506	1.044-6.018	0.04	2.512	1.098-5.743	0.029
Encephalopathy at LRT	1.922	0.856-4.315	0.113	1.626	0.752-3.515	0.217
Hb, g/dL at LRT	0.883	0.694-1.125	0.314	0.883	0.698-1.116	0.297
ABO mismatch	1.795	0.739-4.363	0.197	1.827	0.791-4.220	0.158

DM: Diabetes mellitus; LRT: Liver retransplant; ICU: Intensive care unit; CCI: Charlson comorbidity index; Hb: Haemoglobin; INR: International normalised ratio; MELD: Model for end-stage liver disease; DRI: Donor risk index.



No. at risk	0	90	180	270	360
CCI = 0	63	60	60	60	60
CCI ≥ 1	81	60	53	53	53

Figure 1 One-year waiting list survival according to the presence or absence of comorbidity. Log-Rank = 6.798, *P* = 0.009. CCI: Charlson comorbidity index.



No. at risk	0	90	180	270	360
CCI < 18	63	58	58	58	58
CCI ≥ 18	81	62	49	49	49

Figure 2 Waiting list survivals according to Model for end-stage liver disease score at listing (cut-off value of 18). Log-Rank = 6.741, *P* = 0.009. CCI: Charlson comorbidity index; MELD: Model for end stage liver disease.

PLT and patients who had a second transplant, Log-Rank = 1.741, *P* = 0.187 and Log-Rank = 2.225, *P* = 0.136, respectively. Patients who received ≥ 3 grafts had significantly decreased 5-year survival of 40%

compared to 72% in those who received 1 graft and 64% in patients who received 2 previous grafts (Log-Rank test: 13.737, *P* < 0.001).

With regards to the time interval between liver

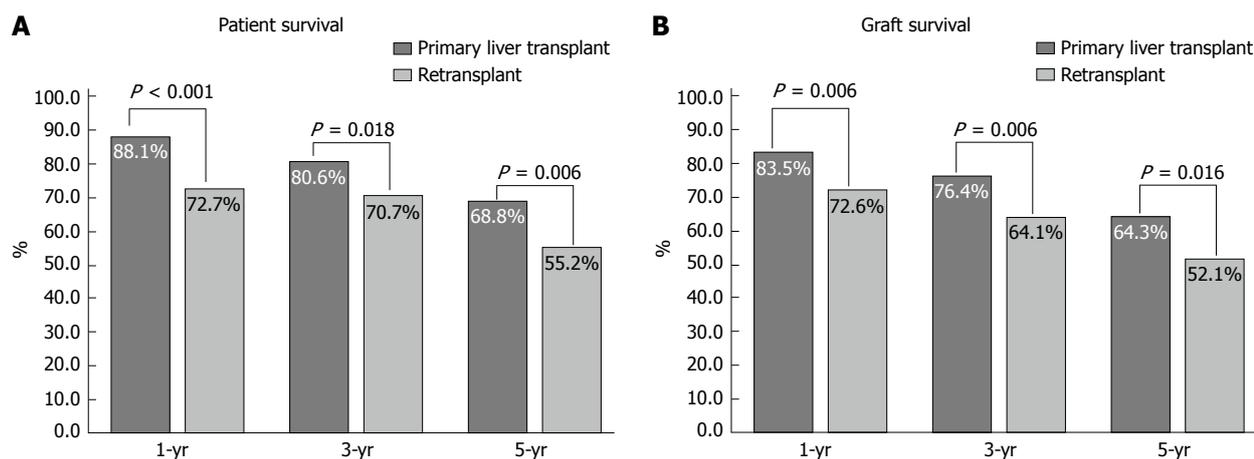


Figure 3 Post-transplant survival at 1, 3 and 5 years. A: Post-transplant patient survival for PLT and LRT; B: Post-transplant graft survival for PLT and LRT. LRT: Liver retransplantation; PLT: Primary liver transplantation.

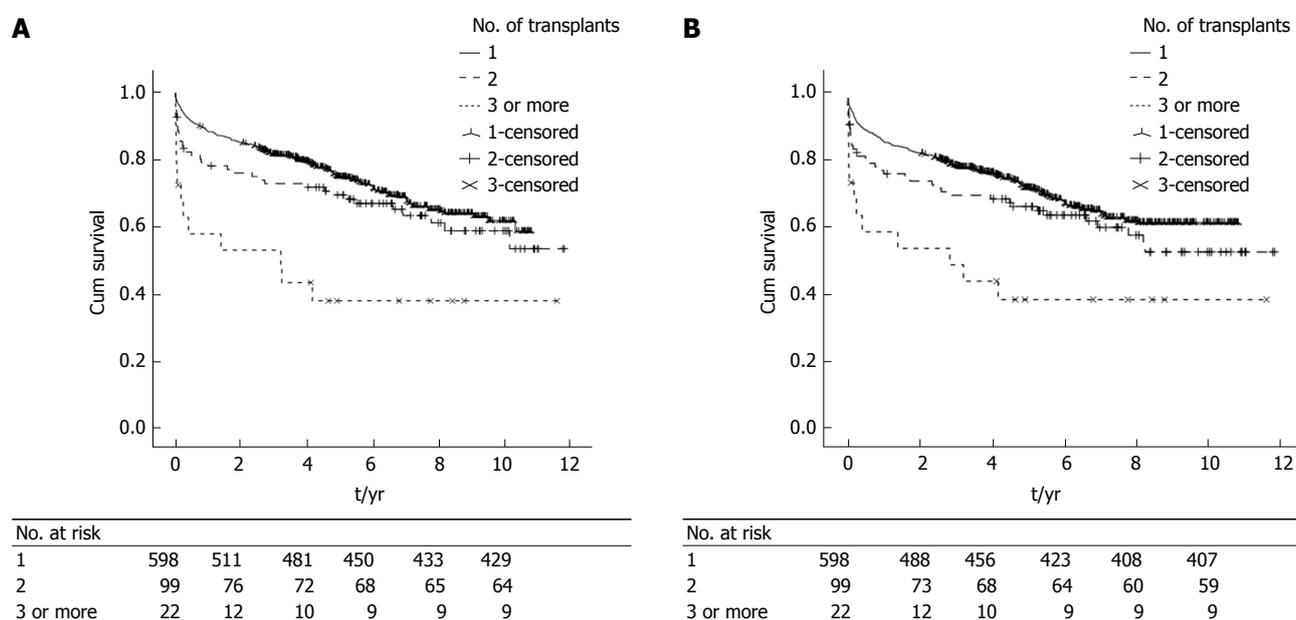


Figure 4 Post-transplant survival according to the number of transplants. A: Kaplan Meier survival analysis of post-transplant patient survival according to the number of transplants. Log-Rank = 18.455, $P < 0.001$; B: Kaplan Meier survival analysis of post-transplant graft survival according to the number of transplants. Log-Rank = 13.737, $P = 0.001$.

transplantation and repeat transplant, patients who were transplanted between day 8-30 had the worse 1-year post transplant survival followed by those transplanted within the first 7 d. Patients who were transplanted > 30 d had significantly improved 1-year post-LRT survival (Log-Rank test: 6.952, $P = 0.031$). Table 4 summarises prognostic variables and indications for LRT according to time interval between transplants. Age, MELD at transplantation and the presence of comorbidity were not significantly different between the groups. Majority of patients who had LRT within 7 d of index transplant had early graft dysfunction. Majority of patients who had LRT 8-30 d of index transplant had vascular complications.

We performed Cox proportional hazard analysis to identify factors associated with post-transplant patient

and graft survival in retransplanted patients. CCI (OR = 2.048, 95%CI: 1.294-3.241, $P = 0.002$), the presence of any comorbidity (HR = 1.920, 95%CI: 1.092-3.373, $P = 0.023$) and requirement for RRT (HR = 1.890, 95%CI: 1.044-3.424, $P = 0.036$) were associated with post-LRT patient survival on univariate analysis. Liver prognostic models (MELD, UKELD), donor or graft variables were not associated with patient survival in retransplanted patients. With regards to graft survival, only vasopressor support prior to LRT was associated with increased graft loss on univariate analysis (HR = 1.974, 95%CI: 1.033-3.744, $P = 0.04$).

Table 3 summarises variables associated with 1-year post-LRT patient and graft survival on Cox proportional hazard analysis. Only the presence of encephalopathy at LRT, Hb level at LRT and ABO

Table 4 Comparison of prognostic variables according to time interval of liver retransplantation

Time between transplants (d)	0-7 (n = 19)	8-30 (n = 16)	> 30 (n = 86)	P value
Age	54 (18-67)	44 (20-63)	43 (19-70)	0.086
Transplant MELD	22 (10-40)	17 (8-36)	17 (6-31)	0.104
CCI \geq 1, n (%)	10 (71)	11 (61)	44 (49)	0.095
Indication, n (%)				
Early graft dysfunction	14 (74)	2 (13)	2 (2)	< 0.001
Graft rejection	0 (0)	1 (6)	30 (35)	< 0.001
Vascular	5 (26)	13 (81)	23 (27)	< 0.001
Disease recurrence	0 (0)	0 (0)	24 (28)	0.001
Other indications	0 (0)	0 (0)	7 (8)	0.106

CCI: Charlson comorbidity index; MELD: Model for end stage liver disease.

mismatch were chosen as fixed variables in the model to avoid cross interaction between variables of similar clinical significance. The CCI, RI, pre-LRT mechanical ventilation, requirement for renal replacement therapy, vasopressor support and listing MELD \geq 18 were independently associated with 1-year patient survival. Similar findings were found for graft survival except for mechanical ventilation which was not associated with outcome.

Graft quality

Median donor age was 44 years (10-76), 55 (45.5%) of donors were males. Donor - recipient gender mismatch was seen in 45 cases (37.2%). Donor ethnicity was Caucasian in 117 (96.7%). Donor cause of death was trauma related in 20 donors (16.5%). Median donor height was 170 cm (147-196), median donor weight was 70 kg (28-110) and BMI was 24 kg/m² (16-34). Only 4 patients received split organs and 1 patient received a graft donated after cardiac death (DCD). Blood group mismatch was seen in 17 cases (14%). Median cold ischemia time was 10.55 h (0.92-19.53) and median DRI was 1.511 (1.0-2.8). There were 24 patients (20.2%) who received marginal grafts (DRI > 1.8). The DRI, or components of DRI in isolation, and DRI > 1.8 were not associated with 12-mo or long-term post-transplant patient or graft survival on Cox proportional hazard analysis.

DISCUSSION

The CCI was originally developed and validated as a tool to predict hospital outcome in general medical patients^[20]. Composed of medical conditions with varying assigned weights, versions of CCI were found to predict outcomes in multiple clinical settings^[21-26]. In this study, we reported on 150 episodes of assessment for LRT from a single centre. We demonstrated that comorbidity as defined by CCI is common (56%) in patients assessed for LRT, and higher than that reported for PLT (40%)^[14]. This high prevalence of comorbidity is mainly attributed to the high prevalence of renal impairment (44%) in this cohort. It is difficult to estimate the rate of renal dysfunction in LRT patients

from previously published studies^[3,4,12,18]. RI was seen in 33% of candidates listed for PLT according to the data of the SRTR^[7].

Renal dysfunction is a well recognised complication in patients with ESLD, critical illness and in PLT^[27-30]. Renal impairment is known to have detrimental impact on survival of patients with ESLD^[31,32]. Therefore, the increased prevalence of RI in our cohort can be explained by the fact that patients listed for LRT have more severe liver dysfunction, reflected by higher MELD scores compared to PLT patients and also by the large proportion of patients who were transplanted from ICU (33%) reflecting the severity of their illness. Furthermore, standard immunosuppression agents with Calcineurin inhibitors such as Cyclosporin or Tacrolimus which is routinely used following liver transplantation to prevent rejection are known to cause or at least contribute to renal impairment following liver transplantation^[33]. Other comorbidities, apart from DM, were rare which may be explained by the relatively young median age of patients listed for LRT compared to PLT. The younger age of LRT patients compared to PLT is consistent with previous reports^[18,34].

This is the first study to demonstrate the impact of comorbidity on WL mortality in LRT patients. The presence of any comorbidity defined by the CCI was independently associated with a greater than 5 times the risk of death on the wait list. Furthermore, this study has shown that the presence of any comorbidity was associated with twice the risk of post-LRT patient death. Similarly, comorbidity was associated with a three-fold increased risk of patient death and two fold increased risk of graft loss within 12 mo post-LRT. The only study to date which investigated the effect of comorbidity on post liver transplant outcome showed that the presence of any comorbidity was associated with 21% increase in patient death following PLT^[14]. Comorbidity was also found to predict post-transplant outcome in patients who received renal and allogeneic stem cell transplantation^[35-38].

We have demonstrated in this study that the median MELD score for patients assessed for LRT was significantly higher compared to PLT patients. We have also shown that the increase in MELD among

LRT candidates was attributable to the high median bilirubin and creatinine levels but not to an increase in INR which is consistent with UNOS data (Table 1)^[34]. We have also shown that the already established models to assess the severity of hepatic impairment (MELD and UKELD) were independently associated with WL mortality. Furthermore, MELD score at a cut-off as low as 18 was associated with WL mortality which was increased by more than 4 fold. This suggests that patients listed for LRT with MELD score ≥ 18 may benefit from prioritization on WL and earlier transplantation to improve LRT outcome.

Our data showed increased WL mortality in LRT patients with MELD score of 18 or higher. In a report from The University of Nebraska, Watt *et al*^[39] showed that MELD score was predictive of WL mortality in 63 patients listed for a second transplant. WL mortality was also shown to increase with increasing MELD scores, especially at the lower range of MELD^[34]. None of the other previously reported studies examined the performance of MELD in predicting WL mortality in LRT patients. Instead, these reports focused on factors predictive of post-LRT outcomes^[2,3,5,11,18,40,41]. Surprisingly, WL mortality was lower for LRT patients (11% vs 24%, $P < 0.001$), discordant to previous reports^[34]. This can be explained by the fact that patients listed for LRT had significantly shorter median waiting time (16 d vs 100 d, $P < 0.001$) which may indicate an informal prioritization mechanism for patients listed for LRT in our hospital. Our report also suggests that UKELD score retains its predictive capacity of WL mortality in patients listed for LRT with a 12% rise in WL mortality with every point increase in the UKELD score. Another important finding of the current study is that recipient age > 60 years was independently associated with death on the WL in LRT patients, consistent with previous studies that identified advanced recipient age as a risk factor for WL mortality in patients listed for PLT^[28,42,43].

We have shown that 1-, 3- and 5-year patient and graft survival were inferior in patients who underwent retransplantation, consistent with previously published reports^[5,13]. This inferior post-transplant survival in our cohort is mainly attributed to the poor post-LRT survival in patients who received ≥ 3 grafts. Patients who had a second graft had slightly lower patient survival compared to PLT. Although these findings contrast with the outcome of patients who underwent retransplantation 1984-2001 at The University of California Los Angeles, improved survival of patients who had a second transplant in our cohort may be explained by both a different era of transplantation, advances made in immunosuppression and local patient selection processes^[13]. Our findings also suggest that a second liver transplant may represent an acceptable use of donated organs in selected patients. However, if we take into consideration the rule of 50% survival benefit at 5 years post-transplant, according to our findings a third or subsequent grafts may not represent

an appropriate use of donated organs, except in rare instances^[6].

Published reports suggested that the time interval between PLT and LRT has an influence on post-transplant outcome. Reports from 2 transplant programs indicated that LRT 4-30 d or 8-30 d following first transplant carries a worse post-transplant survival^[11,13,40]. Our data showed inferior survival in patients who were transplanted within 30 d from previous liver transplantation, irrespective of whether LRT occurred in the first 7 d or between 8-30 d. In our cohort, the most common indication for LRT within the first 7 d following a previous transplant was early graft dysfunction whilst vascular complications (thrombotic and non-thrombotic graft infarction) were the primary indication in patients who had LRT 8-30 d following a previous transplant. This increased post-LRT mortality in patients who receive early LRT may be explained by severity of illness, intense immunosuppression, hence increased risk of infections^[2,44]. Our findings are consistent with those of Rosen *et al*^[18] who reported significantly inferior long term survival in patients who had LRT for PNF and vascular complications. In both United States and the United Kingdom, in recognition of the severity of illness and the high mortality associated with PNF and early HAT without LRT, an urgent priority for LRT is given^[45,46].

Regarding post-LRT survival, we demonstrated that the CCI, RI, MELD score ≥ 18 and requirement for organ support were independent factors associated with 1-year post-LRT patient and graft survival consistent with the reported literature in which MELD, or individual components of MELD, were associated with post-LRT outcome^[2,3,9,10,12,40,41]. Similarly, requirement for mechanical ventilation and renal replacement therapy were found to negatively impact on post-LRT outcome in agreement with the reported literature^[2,5,12,40]. Interestingly, we identified pre-LRT vasopressor support as the only factor associated with long term graft outcome. Vasopressor use was also an independent factor associated with 12 mo post-transplant patient and graft survival. This finding has never been reported in previous studies. The requirement for vasopressors may therefore reflect the severity of recipient illness with hemodynamic instability and it may indirectly suggest the negative impact of graft ischemia on patient and graft survival.

Despite our detailed analysis of donor and graft variables, we found no association between graft quality and post-LRT outcomes. This is likely to reflect our local donor-recipient matching practices demonstrated by the limited use of marginal grafts in this cohort and a low median donor age of 44 years which is well within the confines of non-extended criteria donor parameters. Few studies analyzed the impact of graft and donor factors on post-LRT survival. Whilst Pfitzmann *et al*^[5] found no correlation between graft survival and donor variables, others identified donor age, ethnicity and warm ischemia time as factors

independently associated with inferior outcome^[5,10,40].

Limitations of this study were that it represents a single centre experience; therefore, applicability of the findings on other cohorts may be limited. Secondly, data on immunosuppression were not included in our analysis, although standard immunosuppression was used in all cases except for patients with eGFR < 50 mL/min, a renal sparing regimen of low dose Tacrolimus and interleukin-2 (IL-2) blocker and prednisolone was used preferentially. Indeed, the choice of immunosuppression not only can influence post-transplant outcomes in patients underwent PLT, it can influence the rate of complications related to immunosuppression such as RI which we found as an important factor associated with inferior patient and graft survival^[33,47,48]. Thirdly, we used a version of the CCI tested in liver transplant cohort^[14]. Therefore, the impact of other comorbidities on post-transplant survival such as inflammatory bowel disease, peptic ulcer disease, valvular heart disease or obesity, which were found to affect patient survival, remains unknown given they were not incorporated in the model^[20,49]. Lastly, although the definitions of individual comorbidities were consistent with previous reports, clinical applicability of these definitions maybe limited.

In conclusion, our data indicates that the presence of comorbidity in liver retransplant candidates increases mortality on the WL and following LRT. The severity of recipient liver disease was associated with WL mortality. MELD score was able to discriminate between survival and death whilst on the WL at a lower cut-off value of 18 which suggests that patients undergoing LRT should be transplanted at lower MELD scores. Post-transplant mortality progressively increased according to the number of transplanted grafts; however, the greatest adverse impact was seen after transplanting ≥ 3 grafts with only 40% 5-year survival seen in this group. Graft and donor variables were not found to influence patient or graft survival in this study which may reflect centre-related donor-recipient matching.

COMMENTS

Background

The prevalence and impact of comorbidities on waiting list (WL) and post-transplant survival in patients undergoing liver retransplantation (LRT) is not known. This study evaluates the impact of comorbidity on the above parameters.

Research frontiers

Model for end-stage liver disease (MELD) score > 25, recipient age, creatinine level, bilirubin level, indication for retransplantation, the urgency for LRT, coma episodes, haemoglobin level and the number of fresh frozen plasma units transfused were identified as factors associated with reduced post-LRT survival in a number of studies.

Innovations and breakthroughs

Comorbidity in liver retransplant patients increases mortality on the WL and following LRT. MELD score of ≥ 18 was associated with increased risk of

death on WL and within 12 mo following retransplantation. Post-transplant mortality progressively increased according to the number of transplanted grafts.

Applications

Patients undergoing LRT should be transplanted at lower MELD scores. Assessment of comorbidity in LRT candidates can provide important prognostic information. A third or subsequent grafts may not represent an appropriate use of donated organs, except in rare instances.

Terminology

ALD: Alcohol-related liver disease; CCI: Charlson comorbidity index; CI: Confidence interval; CIT: Cold ischemia time; DBD: Donation after brain death; DCD: Donation after cardiac death; DM: Diabetes mellitus; DRI: Donor risk index; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus infection; ICU: Intensive care unit; IL-2: Interleukin-2; INR: International normalized ratio; LRT: Liver retransplantation; MELD: Model for end-stage liver disease; Na: Sodium; NHS: National Health Services; OR: Odds ratio; PLT: Primary liver transplantation; RI: Renal impairment; SRT: Scientific Registry of Transplant Recipients; UCLA: University of California Los Angeles; UKELD: United Kingdom End-stage Liver Disease; UNOS: United Network of Organ Sharing; WL: Waiting list.

Peer-review

Very well written paper.

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