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ORIGINAL ARTICLE

Reduction in functional ability is significant postliver transplantation compared with matched liver disease and community dwelling controls

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Summary

We compared functional ability and symptom severity in liver transplant recipients and matched chronic liver disease (CLD) and community controls. A total of 103/140 consecutive liver transplant recipients from a single centre (73%) and matched controls completed the patient-reported functional outcome measure: Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire (PROMIS HAQ). Symptoms frequently seen in CLD were quantified by (i) Fatigue Impact Scale (FIS), (ii) Orthostatic Grading Scale (OGS: autonomic dysfunction), (iii) Cognitive Failures Questionnaire (CFQ) and (iv) Epworth Sleepiness Scale (ESS: Daytime somnolence). Liver transplant recipients exhibited significant reduction in function ($P < 0.0001$) across all domains of the PROMIS HAQ suggesting that functional impairment is broad-based. Seventy-seven per cent of all postliver transplants identified some difficulty with activities of daily living. There was no relationship between PROMIS HAQ and liver biochemistry ($r^2 = 0.04$, P = NS) or time since transplant ($r^2 = 0.1$, P = NS). Elevation in PROMIS HAQ (and therefore functional impairment) strongly associated with symptoms, particularly fatigue, cognitive impairment and daytime somnolence. Fatigue severity was independently associated with functional impairment (FIS) (Beta 0.727, $P < 0.0001$). Symptoms or functional ability was not different between liver transplant recipients and matched chronic liver disease controls. Although survival postliver transplantation is improving, our cross-sectional study suggests that functional ability may not improve postliver transplantation. Further study is warranted to address the mechanisms responsible for post-transplant functional impairment and to develop effective rehabilitation regimes to maximize function following liver transplantation.

Introduction

Over the last decade, the improving liver-transplant survival rate has established liver transplantation surgery as a durable therapy that prolongs life for most forms of end-stage liver disease and for some malignant conditions. Historically, the perception of most clinicians has been that liver transplantation is a procedure that, in addition to increasing length of life, through effecting a cure for their underlying liver disease and its associated life-quality impairing symptoms, returns the patient to something close to a normal life. This view has recently begun to be challenged. Although some studies do suggest that there is significant improvement in life quality following liver

transplantation [1], others demonstrate ongoing impairment of life quality postliver transplant [2–4]. A 30-year follow-up study of patients transplanted in one UK centre suggested that patients had a 'satisfactory' quality of life, but did not define what would be considered satisfactory and whether this was a patient- or clinician-derived measure, a key issue given the tendency of physicians to underappreciate the impact of chronic symptoms on life quality [5]. In addition to integrative concepts such as quality of life, some groups have demonstrated that individual symptoms such as fatigue, which are key determinants of impaired life quality, can persist as chronic problems following liver transplantation [6] suggesting that intervention programs may be warranted [7]. Further potential mechanisms for ongoing quality of life impairment following liver transplantation would include the effects of immuno-suppressive drugs and recurrence of underlying disease. Although the impact of individual symptoms such as fatigue is undoubted in clinical scenarios such as chronic liver disease, their measurement in isolation is reductionist in philosophy and can underestimate what matters most to patients, which is their global clinical status. The ultimate expression of such global clinical status is capacity to function in normal life, and approaches are now well described which can formally encapsulate, in a reproducible fashion, functional status.

To date, no studies have considered overall function as an outcome following liver transplantation. Given the increased longevity of patients after liver transplantation, the need to address the issue of the extent to which they can function normally is clear [8,9], as will the development and application of approaches able to improve function if impaired. This study set out to examine functional ability in a sequential cohort of liver transplant recipients at one UK centre and compared it first with community controls and then with matched nontransplanted patients with chronic liver disease. A number of symptoms are increasingly being recognized as impacting upon life quality in association with chronic liver disease, most particularly fatigue, cognitive problems, autonomic symptoms and daytime somnolence. We went on to explore whether these symptoms persist in a post-transplant group and their relationship with function to determine where interventions might best be targeted to improve functional ability.

Methods

Study design

Cross-sectional comparative study was performed in two phases. Phase 1: Functional ability was compared between a group of liver transplant recipients and community controls. Phase 2: Functional ability and its relationship with symptoms were examined in a subgroup of the liver transplant group matched for age, gender and aetiology with a chronic liver disease comparator group.

Subjects

Liver transplant group

All patients who had undergone liver transplantation at Freeman Hospital Newcastle between January 2005 and June 2009 and who were alive at the study point (140 of the 160 patients transplanted during this period) were invited to complete a series of functional assessment and symptom quantification tools.

Community dwelling comparator group

The total transplanted patient group was also matched group-wise on an age- and gender-matched basis with normal community controls who had completed the functional assessment tool. No selection (positive or negative) was made with regard to co-morbidity, fatigue status or functional ability in any of the study groups.

Nontransplanted chronic liver disease comparator group

Each recipient who had undergone liver transplantation for chronic liver disease was matched on a case-by-case basis for disease aetiology, age and gender with the nearest person on our UK NIHR Biomedical Research Centre liver database for comparison in a blinded manner. Patients undergoing transplantation for acute liver failure were included in the post-transplant functional assessment, but were not matched with disease controls because of lack of a relevant comparator. Sixty-eight of the total group proved possible to match from the disease group's alcoholic liver disease, primary sclerosing cholangitis, primary biliary cirrhosis, nonalcoholic steatohepatitis and autoimmune liver disease.

Measures

Five functional and symptom assessment tools were sent by post to liver disease participants. Subjects were asked to complete these measures and return them in a prepaid envelope. The following were the assessment tools and their rationale for inclusion:

Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire (PROMIS HAQ) [10,11]

This tool assessed the functional impact of liver transplantation on subjects by measuring the functional and physical ability of the subjects. The PROMIS HAQ was derived from the HAQ and consists of 20 questions that

ask patients to rate their ability to carry out daily activities on a five-point scale of '0 – without any difficulty' to '4 – unable to do'. The 20 questions are divided into eight domains of physical function: dressing, arising, eating, walking, hygiene, reach, grip and activity. The highest scoring question in each domain is used as the domain score. All eight domain scores are added together, divided by 8 and multiplied by 25 to calculate the total PROMIS HAQ score. Higher scores indicate worse functional ability and therefore greater functional impairment.

Cognitive Failures Questionnaire (CFQ) [12–14]
We have previously reported the importance of cognitive symptoms in the impairment of life quality in chronic liver disease patients. To determine whether liver transplant recipients experienced cognitive symptoms more frequently than matched controls, indicating worse cognitive impairment, the liver transplant group and controls completed the CFQ, a fully validated measure that assesses level of cognitive ability. The presence and severity of cognitive symptoms were compared between the two groups. The CFQ assesses the prevalence of cognitive symptoms by measuring the frequency of cognitive slips or failures occurring in everyday life. The cognitive abilities assessed in the CFQ include memory, attention, concentration, forgetfulness, word-finding abilities and confusion. The questionnaire consists of 25 items covering failures in perception, memory and motor function and asks patients to rate how often these failures occur, on a 5-point Likert scale of 0–4 (0 = never, 4 = very often). The responses for the 25 questions are added together to obtain the total CFQ score. The higher the score, the greater is the cognitive impairment.

Fatigue Impact Scale (FIS) [15]
Studies have previously reported that fatigue is a significant factor in life quality impairment in chronic liver disease patients [16–20]. FIS measures fatigue experienced by patients, and how the fatigue functionally limits them in their lives and activities. FIS assesses patients' perception of how fatigue affects their cognitive, physical and psychosocial functions. This includes the impact of fatigue on their work, family and financial responsibilities, their mood, their reliance on others, their social activities, and on their quality of life. It is made up of 40 items and subjects must rate how badly affected these items are because of fatigue on a 5-point scale ranging from 0 (no problem) to 4 (extreme problem). The total FIS score is calculated by adding all answers from the 40 questions together. Higher scores indicate greater impact of fatigue.

Orthostatic Grading Scale (OGS) [21]
Vasomotor autonomic dysfunction is common in chronic liver disease patients and is strongly associated with both cognitive symptoms and fatigue [19,22–26]. The OGS is a self-report assessment tool consisting of five items, which assess the frequency of orthostatic symptoms, severity of orthostatic symptoms, conditions under which orthostatic symptoms occur, activities of daily living and standing time. Patients are asked to grade each item on a scale of 0–4, 0 being the lowest and 4 the highest. The total OGS score is calculated by adding up the scores from each item. Higher scores indicate greater severity of autonomic dysfunction.

Epworth Sleepiness Scale (ESS) [27]
Sleep disturbance (in particular daytime somnolence) is recognized as a factor in chronic liver disease [19,28]. The Epworth Sleepiness Scale (ESS, possible score range 0–24) was used to assess daytime hyper-somnolence, a score of 10 or more being indicative of significant daytime hyper-somnolence.

Serum biochemistry

All subjects were under long-term follow-up by the Newcastle Liver Unit and were subject to regular renal and liver serum biochemical assessment for clinical management reasons. Biochemical values were directly related in time to functional and symptom assessment.

Data analysis

Analysis was performed using the statistical analysis software Prism 3.0 (Graphpad Prism, CA, USA) and spss (SPSS, NY, USA). It was determined whether data were normally or non-normally distributed. Where data were normally distributed, they are presented as mean ± standard deviation, and comparisons were made between groups using unpaired *t* tests. Where data were non-normally distributed, they are presented as median and range and comparisons were made by Mann–Whitney *U*-test. To determine whether the degree of functional impairment experienced by liver transplant recipients was influenced by the symptoms they experienced, we explored the univariate relationship among functional capacity and the symptom assessment tools of cognitive symptoms, fatigue and autonomic dysfunction. Univariate analysis was performed by correlations using Spearman and Pearson's tests, where appropriate for parametric and nonparametric data. To determine whether the relationships between functional ability and the symptoms experienced by liver transplant recipients (cognitive impairment, fatigue and autonomic dysfunction) are independent of each other, a

multi-variate analysis was performed using the log-rank test. Differences in proportions were determined using chi-square tests. A statistically significant result was considered when $P < 0.05$.

Ethical permission

The liver transplant patient database, and the databases from which the matched controls were selected, have approval from the Newcastle-Upon-Tyne Hospitals NHS Trust Caldicott Guardian. The Caldicott Principles were reviewed at the outset and strictly adhered to during all stages of the study. The databases were interrogated for patient identifiable data only when absolutely necessary. All participants who were contacted had provided prior, fully informed consent to be contacted regarding audit, service evaluation and research purposes. Returning the completed assessment tools implied consent for the use of that data which was anonymized and analysed in such a way that no individual could be identified.

Results

Of the 140 live liver transplant recipients who had undergone transplantation during the study period, 103 (74%) returned fully completed function and symptom assessment tools. The demographic and clinical characteristics of this group are shown in Table 1. Compared with age- and gender-matched community controls, the postliver transplant group exhibited greater variability and overall significant functional impairment (Fig. 1). Impact was seen for all domains of the PROMIS HAQ, suggesting that functional impairment is broad-based (Table 2). Seventy-seven per cent of all postliver transplants identified some difficulty with activities of daily living. When we explored factors that associated with poor function postliver transplant no relationship was seen between PROMIS HAQ and liver biochemical markers with albumin and alkaline phosphatase both $r^2 = 0.04$, P = NS, degree of renal impairment) tacrolimus dose or length of time following transplant ($r^2 = 0.1$, P = NS). In marked contrast, elevation in PROMIS HAQ (and thus functional impairment) was strongly associated with the level of systemic symptoms related to fatigue, cognitive impairment and daytime somnolence (Fig. 2).

A multi-variate model was then developed to determine what factors independently predicted functional impairment in liver transplant recipients. A regression model was developed that included all parameters considered

Table 1. Characteristics of the liver transplant group and the normal controls at the point of study.

	Liver transplant group	Community controls
n	103	81
Age (years, mean ± SD)	58 ± 11	61 ± 11
Females (%)	37 (36)	29 (36)
Albumin (g/l)	43 ± 3.8	–
Bilirubin (μM)	11 ± 7.1	–
ALP (U/l)	137 ± 103	–
ALT (U/l)	37 ± 34	–
PROMIS HAQ	22.8 ± 27	5.8 ± 14
FIS	54.5 ± 42	–
COG-FAIL	38 ± 25.2	–
ESS	8.7 ± 6	–
OGS	4.5 ± 5.0	–
Tacrolimus therapy (%)	82	–
Mean dose	3.3 ± 2.5	
Time since transplant (months), median and range	40 (2–155)	–

ALP, alkaline phosphatase; ALT, alanine transaminase; ESS, Epworth Sleepiness Scale; FIS, Fatigue Impact Scale; PROMIS HAQ, Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire; OGS, Orthostatic Grading Scale.

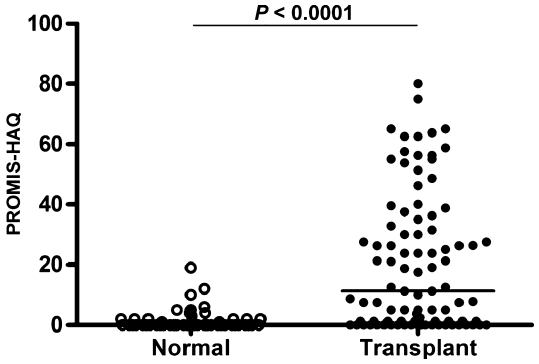

Figure 1 Total Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire (PROMIS HAQ) scores in a comprehensive cohort of liver transplant recipients and matched normal controls.

Table 2. Median (IQR) Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire (PROMIS HAQ) scores for the individual domains of functional ability.

	Normal controls	Liver transplant	*P*
Dressing	0 (0–0)	0 (0–2)	<0.01
Arising	0 (0–0)	1 (0–2.5)	<0.0001
Eating	0 (0–0)	0 (0–1)	0.05
Walking	0 (0–30	1 (0–4)	<0.001
Hygiene	0 (0–2)	1 (0–4)	<0.001
Reach	0 (0–0)	1 (0–3)	<0.001
Grip	0 (0–0)	0 (0–1)	0.01
Activity	0 (0–0)	2 (0–3)	<0.001

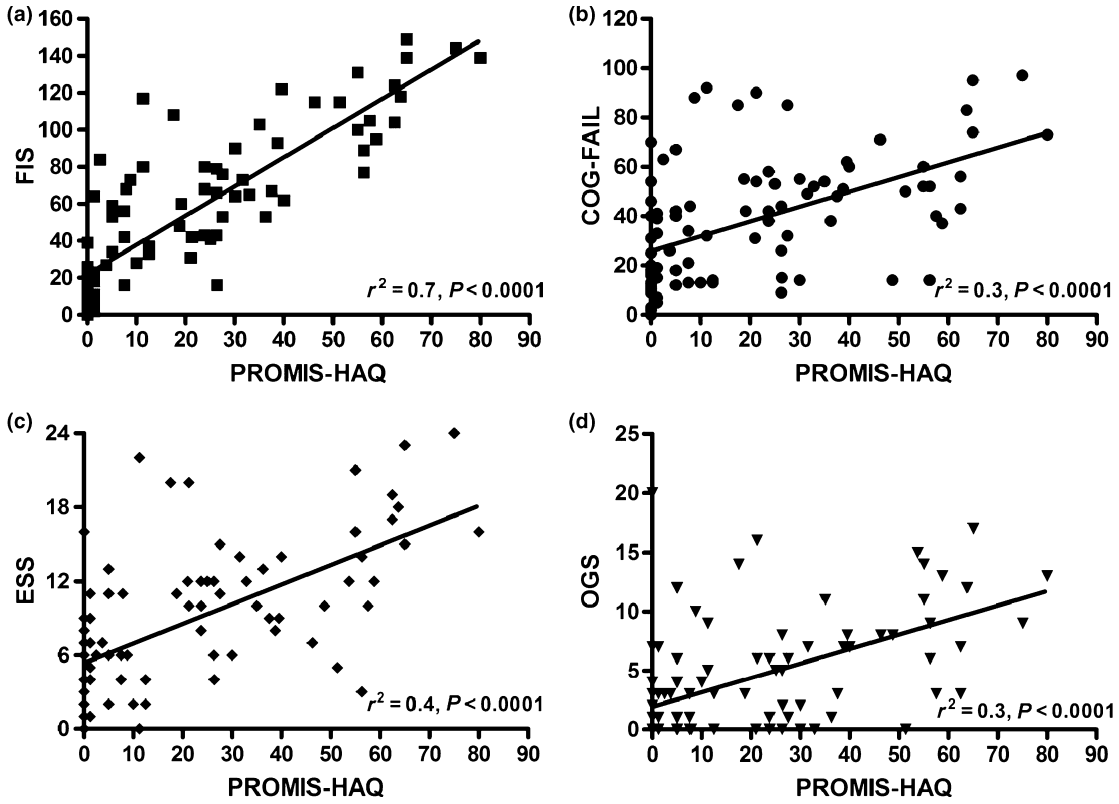

Figure 2 Correlation between Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire (PROMIS HAQ) and (a) Fatigue severity as assessed by Fatigue Impact Scale (FIS), (b) Cognitive symptoms as assessed by COG-FAIL, (c) Daytime somnolence as assessed by Epworth Sleepiness Scale (ESS), (d) Orthostatic autonomic dysfunction symptoms, as assessed by Orthostatic Grading Scale (OGS) in liver transplant recipients.

important including age, months since transplant, liver function tests (alkaline phosphatase, alanine transaminase, bilirubin, albumin), symptoms including fatigue (FIS), autonomic symptoms (OGS), cognitive symptoms (COG-FAIL) and daytime somnolence (ESS). The only factor independently associated with degree of functional impairment was fatigue severity as quantified by FIS ($B = 0.496$, SE 0.095, Beta 0.727, $P < 0.0001$) (Table 3a).

A total of 68 patients were transplanted for end-stage chronic liver disease and could be matched with equivalent nontransplanted patients of the same age and gender with the same underlying disease aetiology. There were no significant differences in symptoms or functional ability between those who had undergone liver transplantation compared with chronic liver disease patients with the same aetiology who had not undergone transplantation (Table 4). In contrast, significant improvements in liver function tests were, unsurprisingly, seen in the postliver transplant group. When a comparable multivariate model was performed in the chronic liver disease control group, there were no independent predictors of function (Table 3b).

Discussion

Over the last decade, an improving liver transplant survival rate has been instrumental in establishing liver transplantation surgery as a durable and effective therapy for end-stage liver disease. Improvements in surgical technique and immuno-suppressive medication have meant that the outcomes from liver transplantation in terms of length of life after surgery have improved continuously. The extent to which transplantation is equally effective in resolving symptoms, improving life quality and returning function to normal has been less well studied, although the presumption has always been that function following liver transplant is good, if not normal [1–6]. In this study, we have used a broad-based and widely accepted measure of functional status in a comprehensive cohort of liver transplant patients within 4 years of transplantation. Our findings suggest that function is far from being normal or even close to normal, and is impaired across all domains. Furthermore, the difficulties experienced by liver transplant patients with regard to function are associated not with parameters suggestive of liver dysfunction

Table 3. Predictors of function (Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire, PROMIS HAQ) in (a) the post-transplant group and (b) the chronic liver disease control group.

Model	*B*	SE	Beta	Sig.	95.0% confidence interval for *B* Lower	Upper
(a)						
Model 1 (Constant)	9.094	35.857		0.801	−62.891	81.080
Age	0.035	0.288	0.012	0.903	−0.543	0.613
Albumin	−0.273	0.703	−0.037	0.700	−1.685	1.139
Bilirubin	0.068	0.356	0.018	0.849	−0.647	0.783
ALP	0.006	0.026	0.025	0.802	−0.045	0.058
ALT	−0.117	0.083	−0.140	0.167	−0.283	0.050
FIS	0.496	0.095	0.727	0.000	0.304	0.688
OGS	0.602	0.657	0.107	0.365	−0.718	1.921
COG-FAIL	−0.050	0.157	−0.043	0.751	−0.365	0.265
Months since OLT	−0.066	0.090	−0.069	0.463	−0.247	0.114
(b)						
Model 1 (Constant)	270.911	65.932		0.152	−566.829	1108.651
Age	−1.386	0.638	−0.676	0.275	−9.489	6.718
Albumin	−2.595	0.758	−0.701	0.181	−12.222	7.031
Bilirubin	−0.735	0.275	−0.712	0.228	−4.226	2.755
ALP	−0.072	0.044	−0.756	0.348	−0.628	0.484
ALT	0.091	0.460	0.066	0.876	−5.760	5.941
FIS	−0.206	0.181	−0.330	0.458	−2.504	2.091
OGS	9.951	1.484	1.284	0.094	−8.901	28.803
COG-FAIL	−1.431	0.388	−1.190	0.169	−6.365	3.503

ALP, alkaline phosphatase; ALT, alanine transaminase; FIS, Fatigue Impact Scale; OGS, Orthostatic Grading Scale.

Table 4. Comparison between the liver transplant group and matched chronic liver disease (CLD) group (matching was for aetiology, age and gender).

	Liver transplant	Matched CLD	*P*
N	68	68	
Age	58 ± 11	59 ± 10	0.2
Males (%)	41 (60)	41 (60)	NS
Aetiology (%)			
ALD	34 (50)	34 (50)	NS
PSC	15 (22)	15 (22)	
PBC	13 (19)	13 (19)	
NASH	5 (7)	5 (7)	
AIH	1 (2)	1 (2)	
PROMIS HAQ	18.6 ± 23	18.5 ± 23	0.9
FIS	57 ± 44	62 ± 45	0.12
COG-FAIL	40 ± 27	41 ± 25	1.0
Bilirubin	10.3 ± 6.2	17 ± 15.6	**0.0021**
Albumin	43 ± 3.8	42 ± 5.3	**0.05**

Data shown are mean ± SD unless otherwise stated. Bold indicates statistically significant differences.

ALD, alcoholic liver disease; FIS, Fatigue Impact Scale; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; PROMIS HAQ, Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire; NASH, non-alcoholic steatohepatitis; AIH, autoimmune liver disease; CLD, chronic liver disease.

or transplant associated co-morbidity such as renal impairment or immuno-suppression, but rather with those systemic symptoms increasingly recognized in those with chronic liver disease notably fatigue, cognitive symptoms, autonomic symptoms and daytime somnolence. The particular importance of fatigue (the only parameter independently associated with functional ability in liver transplant patient recipients on multi-variate analysis) suggests that this symptom should be a particular target for study if we are to understand why function is impaired post-transplant and if we are to significantly improve it. Recent studies in patients with liver disease have confirmed that with a structured approach to fatigue management, this symptom can be improved [29], and we would suggest that similar approaches in post-transplant liver patients have the potential to deliver the same outcomes.

The question of life quality following liver transplantation and the expectations that patients could hold are of particular importance given the increasing recognition of the impact that chronic liver disease itself has on life quality and function prior to transplant [8]. Given the poor life quality typically experienced by patients with advanced liver disease, the expectation of improvement or normalization in life quality and function after transplant is understandable and is, anecdotally, a factor in patients pursuing the option of liver transplantation. The extent of symptom, life quality and function improvement following liver transplantation is, however, very controversial with a contradictory and flawed existing literature. Whilst some studies suggest that quality of life is 'satisfactory' in postliver transplant groups, others document significantly impaired quality of life [1–8]. Closer examination of the literature identifies a number of factors, which may explain discrepancies and which highlight a number of key issues. The first factor is that important differences exist between outcomes in terms of specific isolated symptoms such as encephalopathy or cholestatic itch (which typically improve compared with pretransplant) and broader life quality (which appears to improve less). One potential explanation could be that focus on pretransplant symptoms and their improvement following transplant discounts the potential impact on quality of life of new symptoms arising post-transplant related to surgical morbidity and the systemic effects of immuno-suppressive drugs. The important concept of function has as yet not been considered as an outcome in liver transplantation. Defining outcome in the narrow terms of those symptoms,

which might be predicted to improve whilst discounting the negative impact of new symptoms directly related to the transplant process, is likely to overstate significantly the benefits of transplantation. It is important to begin to acknowledge that patients who have undergone a liver transplant are a chronic disease group and will require support and ongoing clinical management.

The second important factor which could help explain discrepancy in outcome data is the difference between comparison of baseline rather than comparison of control. Most studies show improvement in quality of life compared with pretransplant status, whilst patients are interested in whether they return to normal. This could lead to a significant discrepancy between clinician and patient perception of outcome with the former deeming the transplant a success (improvement compared with pretransplant) and the latter a relative failure (not back to normal).

The third potential factor is a failure to address temporal effects. There appears to be a temporal element to perception of life quality following transplant in the literature, with longer term follow-up being characterized by worse perceived outcome [5]. This might be a real effect (cumulative impact of drugs) or a perception issue (in the early post-transplant patient, the perception of improvement compared with pretransplant might predominate, whilst many years later, when the memory of pretransplant symptoms fades, the perception of non-normality might predominate.

Although our study suggests that reduced function occurs across all domains, it is not clear as to what the mechanisms are whereby liver transplant affects an individual's functional ability, and whether these mechanisms are potentially modifiable. Studies confirm clustering of post-transplant patient experience (some patients doing well and others not) suggesting that there may indeed be an opportunity to intervene with rehabilitation in the pretransplant period with the ultimate outcome of improving functional ability and quality of life [30,31]. Potential mechanisms for the deficits would include ongoing processes from the pretransplant period, which fail to improve with transplantation (for example, organic brain injury which can arise in the context of chronic liver disease and be associated with neurophysiological dysfunction which itself appears not to improve with transplant). Effects of immuno-suppressive drugs and the impact of recurrent disease would appear less likely as causes given the lack of association with tacrolimus dose and the relatively early post-transplant time spread seen in our study.

This study has its limitations; it is clearly a cross-sectional study, and performing a longitudinal study would be of great value in exploring functional ability over time in this patient group. This not withstanding, however, we believe, our study indicates that it is now timely to ask the question: is life quality and function normal after a liver transplant, and how might it be improved? The point of this is not to question whether transplantation is valuable (it obviously saves lives), but to help understand what is (and is not) achievable for patients to help them make decisions about transplant, and to devise ways to help patients after transplant by improving function through the development of rehabilitation regimes. Our study did not include evaluation of psychosocial variables or evaluate physical activity, which is a limitation considering the potential for these to impact upon function and quality of life. Furthermore, although our response rate is reasonable, it could be argued that our results may reflect a degree of selection bias and limit the generalizability of our results.

We suggest that studies are needed that perform a comprehensive and patient-centred assessment of the experiences of people undergoing liver transplant to address the degree of post-transplant functional impairment experienced by liver transplant patients, to allow identification of the issues impacting post-transplant function, to undertake an assessment of the attitudes of clinicians and other stakeholders to the issue of post-transplant function and to determine the factors associated with good post-transplant function to allow the development of enhanced care packages to optimize function.

Authorship

CE: collected and analysed the data. DEJ and JN had the original idea for the study, analysed the data and produced the initial drafts of the manuscript. JF: performed the multivariate analysis and collected the data. JP: collated the databases and coordinated the study. All authors have read and approved the final manuscript.

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