ORIGINAL ARTICLE

The effect of liver transplantation on patient-centred outcomes: a propensity-score matched analysis

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SUMMARY

It is unclear whether liver transplantation confers an increase in health-related quality of life (HR-QoL) across all dimensions of health. This study aimed to estimate the effect of liver transplantation on HR-QoL. Pre- and post-transplantation patients attending an outpatient clinic were invited to complete the condition-specific 'Short form of liver disease QOL' questionnaire. Mixed-effect linear regression and propensity-score matching (PSM) on pretransplantation characteristics were used to estimate the difference in overall HR-QoL associated with transplantation. Of 454/609 (74.5%) eligible patients who were included in the analysis, 102 (22.5%) patients fall under pretransplantation category, and 352 (77.5%) were under post-transplantation category. Overall HR-QoL post-transplantation significantly increased in patients without hepatocellular carcinoma (HCC) ($\beta = 16.84$, 95% CI: 13.33 to 20.35, $P < 0.001$), but not with HCC ($\beta = 1.25$, 95% CI: −5.09 to 7.60, $P = 0.704$). Donation after circulatory death (DCD) organ recipients had a significantly lower HR-QoL ($\beta = -4.61$, 95% CI: −8.95 to −0.24, $P = 0.043$). Following PSM, transplantation was associated with a significant increase in overall HR-QoL (average treatment effect: 6.3, 95% CI: 2.1–10.9). There is a significant improvement in HR-QoL attributable to transplantation in this cohort. Post-transplantation HR-QoL was affected by several factors, including HCC status and DCD transplantation, which has important implications for counselling prior to liver transplantation.

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Introduction

Liver transplantation remains the sole therapeutic intervention with curative potential for end-stage liver disease [1]. With sustained improvements in operative technique and postoperative management, survival after transplantation has continued to improve in recent decades. In the UK in 2014/15, 1-year and 5-year survival was reported to be 92.4% and 80.1%, respectively [2]. Liver transplantation has been an endeavour primarily focussed on saving life, yet with its success comes an increasing need to understand its impact on quality of life [3]. This is particularly important in the small number of patients who undergo liver transplantation with the primary aim of improving quality of life, for instance, those with intractable itch or polycystic liver disease. In the early period

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after transplantation, quality of life is influenced by the surgery itself, any associated complications, and the overall trajectory of recovery [4]. In the longer term, quality of life can clearly be affected by graft failure, disease recurrence and the complications of immunosuppressive medication, such as infection, malignancy, nephrotoxicity and cardiovascular complications [5].

Patient-centred outcome measures and health-related quality of life (HR-QoL) are increasingly being recognized as essential for comprehensive surgical outcome evaluation [6,7]. These can assess the physical, psychological, emotional and social dimensions of health. Several liver transplantation-specific instruments have been developed in recent decades [8] and have been used to compare pre- and post-transplantation HR-QoL [9–13]. These studies have demonstrated that liver transplantation provides an overall benefit to quality of life; however, there remains uncertainty around whether this improvement is across all aspects of health. Furthermore, questions remain over the relationship between HR-QoL and time from transplantation [14,15], retransplantation [16,17], and the use of donation after circulatory death (DCD) liver allografts [18–20].

From a patient's perspective, the postinterventional quality of life can be of greater importance than the quantity of life gained [21]. As such, there is a clear mandate to provide robust evidence regarding post-transplantation HR-QoL, in addition to morbidity and mortality. This would allow patients to make fully informed decisions on their healthcare and to evaluate postoperative outcomes more completely. Therefore, this study aimed to estimate the effect of liver transplantation on the health-related quality of life of patients.

Methods

Population

Consecutive patients attending the Scottish Liver Transplantation Unit for an outpatient clinic or waiting list assessment between 16th July and 3rd September 2015, and 15th August and 14th September 2017 were invited to take part. This enabled an interval cross-sectional assessment of those attending. Patients were eligible if over 18 years of age, and not being considered for living liver donation.

Data collection

The validated 'Short form of liver disease quality of life' (SF-LDQOL) questionnaire [9] was used to assess the condition-specific HR-QoL of eligible patients, after verbal consent was obtained. This includes 36 items distributed over nine domains: symptoms of liver disease, effects of liver disease, concentration/memory, health-related distress, sexual function, quality of sleep, loneliness, hopelessness and stigma of liver disease. In addition, this provides an overall HR-QoL score. Formal institutional ethical approval was not required as this study was considered a service evaluation, otherwise involving routinely collected data.

Statistical analyses

Patient characteristics were summarized to compare differences between the two groups. Continuous data were summarized as a mean and analysed using the appropriate parametric tests. Categorical data were cross-tabulated, and differences in proportions were tested using chi-squared (X^2) or Fisher's exact tests. Statistical analyses were conducted in R v3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The threshold of statistical significance was set at $P < 0.05$ *a priori*.

All questionnaire responses were assigned a value based upon the original Likert scale [9], and summated into a mean score for each domain (scaled to a value out of 100). All domains were equally weighted before being summated into a mean overall score.

Mixed-effect linear regression model

Differences in overall HR-QoL were adjusted using a mixed-effect linear regression model. Variables used as fixed effects included: age (years); sex (male, female); ethnicity (white, nonwhite); blood group (O or non-O); body mass index (BMI); pretransplantation Model of End-Stage Liver Disease (MELD) category (<10, 10–15, 15–20, >20); primary liver disease (alcoholic, cholestatic, nonalcoholic fatty liver disease (NAFLD), viral (hepatitis B or C), or other aetiology); and hepatocellular carcinoma (HCC) status (present, absent). These are routinely collected in patients assessed for transplantation at UK Liver Transplant Units and could plausibly affect HR-QoL or time to transplant. First-order interactions were checked and included in the model if found to be influential, with final model selection performed through minimization of the Akaike information criterion. Repeat questionnaires from the same individual who had attended during both periods were modelled as a random effect. A subgroup analysis was conducted on post-transplantation patients to describe the association with organ type (donation after brain death (DBD) or donation after

circulatory death (DCD) organ), number of transplantations received (first transplantation or re-transplantation), and time since transplantation (years). All effect estimates were presented as beta-coefficients, alongside the corresponding 95% confidence interval.

Propensity-score matching

Propensity-score matching (PSM) was used to minimize selection bias and balance variables between pre- and post-transplantation groups. The propensity score was defined as the probability that a patient would be assigned to a particular group (pre- or post-transplantation) depending on the observed characteristics for an individual [22]. Pretransplantation patients were matched with post-transplantation patients based on the same fixed variables as in the mixed-effect linear regression model. Patients without complete data for all matching variables were excluded from the analysis, and the remainder were assigned to pre- or post-groups and matched according to their propensity score.

Full propensity-score matching [23,24] was used, and this subclassification method matches one or more controls to each treated patient. A weighting is applied to each control patient to minimize the average of the estimated distance measure (log odds of being transplanted) between the treated patient and the controls. The weightings for the control patients sum to one and are incorporated as a weighted-regression. This allows more control patients to contribute to the model compared with a simpler "greedy" matching algorithm, such as nearest-neighbour. Patients who appear as a case and a control (e.g. patients with repeated questionnaires who received a transplant in the interim) were not included in the matching procedure, but were simply included one-to-one, together with a random-effect assignment to account for the fact they are the same patient. The balance in factors between groups was assessed before and after matching via the absolute standardized mean difference [22]. A value <0.2 was considered to indicate a covariate was well balanced between treatment groups; however, differences were not tested [25].

The overall average treatment effect (ATE) is defined as the estimated average effect on the HR-QoL of the whole sample being transplanted (e.g. equivalent to the quantity of interest in a randomized control trial) [22], not just those who were transplanted. This summary measure of treatment effect is an average of the *average treatment effect on treated (ATT) and average treatment effect on controls (ATC)*, and was chosen to reflect that patients who undergo transplant are not the same as the population on the waiting list. The ATT was determined through use of known predictors of quality of life in a regression in the propensity-score matched dataset using *pretransplantation (control) patients alone.* We then simulate expected values for quality of life metrics using these coefficients in the *post-transplantation (treated) patients alone.* This gives us an estimate of the counterfactual – what would the quality of life be in the treated patients had they not undergone transplantation. We then compare the observed quality of life in the transplant patients and compare this with the expected quality of life to give a robust ATT. The converse was performed to derive the ATC in the cohort.

Results

Patient characteristics

There were 609 patients eligible for inclusion over both study periods (Fig. 1). Of these, 488 (80.1%) completed the questionnaire, and response rates were similar across period 1 (81.8%, $n = 306$), and period 2 (77.4%, $n = 182$). Overall, 74 (12.2%) refused participation, and 47 (7.7%) were not encountered. Patients were subsequently excluded based on questionnaire incompleteness ($n = 16$, 2.6%) or missing matching variable data ($n = 18$, 3.0%). Therefore, 454 patients (74.5%) were included in the final analyses, with 102 respondents (22.5%) being pretransplantation, and 352 (77.5%) being post-transplantation (Table 1). Fifty-three patients had repeated questionnaires – 11 had received a transplantation since 2015, with others continuing to be pretransplantation ($n = 1$) or post-transplantation ($n = 41$). Within the sample, the most common primary liver diseases were alcoholic (24.0%), cholestatic (22.5%), viral (14.8%) and cholestatic liver disease (11.2%). A description of primary liver diseases included within the "other" category is provided in Table S1.

Average follow-up time of post-transplantation patients was 4.3 years (SD = 5.0), with 114 (32.4%) under 1 year, 132 (37.5%) 1 to 5 years, and 106 (30.1%) over 5 years since transplantation.

Mixed-effects linear regression

The overall unadjusted HR-QoL score was 13.3 (95% CI: 9.6 to 17.1, $P < 0.001$) points higher in the post-transplantation group compared with the pretransplantation group. There was a significant 1st order

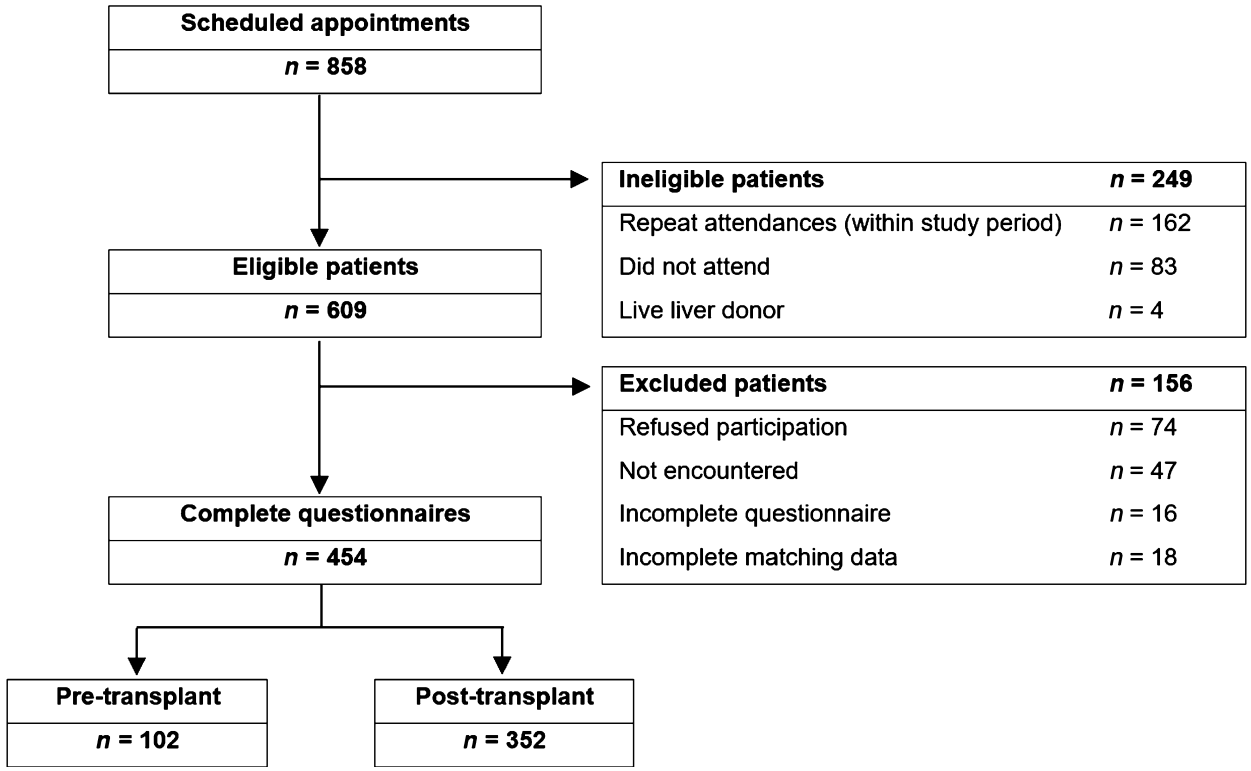

Figure 1 Flow diagram of patient inclusion.

interaction between transplantation and HCC status on overall HR-QoL ($P < 0.001$), and so this was included as a composite variable in the mixed-effect linear regression model (Table 1). There was a persistent increase in overall HR-QoL associated with transplantation in non-HCC patients after adjustment ($\beta = 16.84$, 95% CI: 13.33 to 20.35, $P < 0.001$). However, there was no significant difference in HR-QoL associated with transplantation in patients with HCC ($\beta = 1.25$, 95% CI: −5.09 to 7.60, $P = 0.704$). Subgroups within the post-transplantation group were also compared (Table 1). Following adjustment, receipt of a DCD-organ was associated with a significantly lower post-transplantation HR-QoL ($\beta = -4.61$, 95% CI: −8.95 to −0.24, $P = 0.043$) compared with receipt of a DBD-organ. In contrast, the overall HR-QoL remained consistent over time for post-transplantation patients, and on re-transplantation.

Propensity-score matching

Balance diagnostics

The baseline characteristics of pre- and post-transplantation respondents were explored before and after propensity-score matching (Table 2). In the unmatched, there was a higher proportion of males, higher mean BMI, different distribution of primary liver diseases, and lower MELD score in pretransplantation patients. However, following propensity-score matching, there was a substantial improvement in the balance of most variables, with standard mean difference (SMD) ≤0.2 for all variables.

The level of missingness in the questionnaire responses was <1% for all variables included in the analysis, with the exception of the effect of liver disease on housework (20%) or travel (18%), effect of medications (16%) and libido (10%). Three questions (9a, 9b, 10) related to sexual function were excluded because of levels of missingness > 20%.

Results

In the unmatched sample, pretransplantation patients rated the health-related distress domain significantly lower, and the perceptions of loneliness significantly higher than the overall score (Table 3; Fig. 2). However, following PSM and multivariable adjustment, no substantial differences were observed. Similarly, post-transplantation patients rated quality of sleep

Table 1. Descriptive statistics and mixed-effects linear regression for overall SF-LDQOL score by transplantation status and post-transplantation subgroup. Variables modelled as fixed effects are presented in the table, with repeated questionnaires modelled as a random effect.

		Overall health-related quality of life score for the SF-LDQOL questionnaire					
		All patients (n = 453)			Post-transplantation group (n = 352†)		
		Descriptive statistics*	β coefficient (95% CI)	P	Descriptive statistics*	β coefficient (95% CI)	P
Transplantation and HCC status	Pretransplantation with no HCC	75 (16.5)	Reference category	-	-	-	-
	Pretransplantation with HCC	27 (5.9)	12.84 (6.51 to 19.15)	<0.001	-	-	-
	Post-transplantation with no HCC	277 (61.0)	16.84 (13.33 to 20.35)	<0.001	-	-	-
	Post-transplantation with HCC	75 (16.5)	14.19 (9.30 to 19.08)	<0.001	-	-	-
Age (years)	Mean (SD)	55.7 (13.1)	0.18 (0.07 to 0.30)	0.003	56.2 (13.1)	0.18 (0.05 to 0.30)	0.008
Sex	Male	256 (56.4)	Reference category	-	190 (54.0)	Reference category	-
	Female	198 (43.6)	−3.59 (−6.46 to −0.73)	0.016	162 (46.0)	−2.95 (−6.00 to 0.09)	0.064
Ethnicity	Caucasian	431 (94.9)	Reference category	-	335 (95.2)	Reference category	-
	Non-Caucasian	23 (5.1)	−0.55 (−6.86 to 5.76)	0.866	17 (4.8)	−1.64 (−8.88 to 5.60)	0.664
BMI (kg/m^2)	Mean (SD)	27.6 (5.7)	−0.01 (−0.25 to 0.23)	0.915	27.4 (5.5)	−0.16 (−0.42 to 0.11)	0.255
Blood group	O	239 (52.6)	Reference category	-	176 (50.0)	Reference category	-
	Non-O	215 (47.4)	0.15 (−2.62 to 2.92)	0.917	176 (50.0)	0.43 (−2.58 to 3.44)	0.786
Primary liver disease	Other ‡	125 (27.5)	−1.97 (−5.82 to 1.89)	0.323	101 (28.7)	Reference category	-
	Alcoholic	109 (24.0)	−0.49 (−4.32 to 3.35)	0.804	82 (23.3)	−3.57 (−7.79 to 0.67)	0.106
	Cholestatic	102 (22.5)	−2.36 (−7.44 to 2.73)	0.370	81 (23.0)	−1.26 (−5.44 to 2.93)	0.564
	NAFLD	51 (11.2)	−4.45 (−9.09 to 0.18)	0.064	35 (9.9)	−0.99 (−6.75 to 4.77)	0.741
	Viral	67 (14.8)	−1.97 (−5.82 to 1.89)	0.323	53 (15.1)	−4.89 (−10.06 to 0.27)	0.070
HCC status	Present	-	-	-	75 (21.3)	Reference category	-
	Absent	-	-	-	277 (78.7)	2.32 (−1.86 to 6.53)	0.288
MELD score	<10	62 (13.7)	Reference category	-	37 (10.5)	Reference category	-
	10–15	105 (23.1)	0.41 (−4.40 to 5.25)	0.869	78 (22.2)	1.03 (−4.51 to 6.62)	0.722
	15–20	100 (22.0)	−0.65 (−4.38 to 3.09)	0.738	78 (22.2)	−1.80 (−5.96 to 2.35)	0.406
	> 20	187 (41.2)	−0.50 (−3.60 to 2.61)	0.754	159 (45.2)	−0.44 (−4.12 to 3.24)	0.818
Time since transplantation	Mean (SD)	-	-	-	4.3 (5.0)	−0.18 (−0.52 to 0.16)	0.307

Table 1. Continued.

		Overall health-related quality of life score for the SF-LDQOL questionnaire					
		All patients (n = 453)			Post-transplantation group (n = 352†)		
		Descriptive statistics*	β coefficient (95% CI)	P	Descriptive statistics*	β coefficient (95% CI)	P
Re-transplantation status	First transplant	-	-	-	307 (87.2)	Reference category	-
	Re-transplant	-	-	-	45 (12.8)	−2.88 (−7.45 to 1.68)	0.227
Type of organ	DBD-organ	-	-	-	300 (85.5)	Reference category	-
	DCD-organ	-	-	-	51 (14.5)	−4.61 (−8.95 to −0.24)	0.043

BMI, body mass index; DBD, donation after brain death; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.

*Values in parentheses are percentages unless indicated otherwise.

†n = 1 record excluded because of missing data.

‡See full list of included conditions in Table S1.

significantly lower, and social stigma and loneliness significantly higher than the overall score (Table 3; Fig. 2). However, this persisted following matching and multivariable adjustment in all cases except loneliness. The Average Treatment Effect on the overall score was estimated to be 6.3 (95% CI: 2.1–10.9). The ATE for each questionnaire domain was also investigated (Table 3; Fig. 3), with significant improvements in HR-QoL attributable to transplantation across all domains bar cognition which did not demonstrate a significant change in this cohort (ATE: 3.3, 95% CI: −0.6 to 7.4). Other measures of treatment effects, including the average treatment effect on the treated (ATT) and the average treatment effect on the control (ATC), are presented in Table S2.

Discussion

With continuing improvements in patient and graft survival post-transplantation in recent years, the definition of success in liver transplantation has increasingly focussed on the long-term quality of life for patients. This study aimed to estimate the effect of liver transplantation on the HR-QoL of patients. To the best of our knowledge, it represents one of the largest quality of life studies in liver transplantation patients conducted to date [3]. This is the first study to utilize propensity-score matching to answer this question, which allowed causal inference of the effect of liver transplantation on quality of life within the context of an observational study. As observed in previous studies on the topic [9,14,26], these results show a significant improvement in overall self-reported health in post-transplantation patients (ATE: 6.3, 95% CI: 2.1 to 10.9). This is the first time the change in quality of life attributable to liver transplantation has been quantified in this manner. This study also describes the association between quality of life and a variety of pre- and post-transplantation factors which represent important considerations in counselling of pretransplantation patients.

While there is evidence to support an overall improvement in HR-QoL after transplantation in general [3,14,26,27], there continues to be uncertainty whether this is across all aspects of health. The heterogeneity of instruments utilized in the literature to assess HR-QoL in liver transplantation patients has been a factor, given the challenges in directly comparing these results. Nevertheless, the physical aspects of health in liver transplantation patients appear to show consistent improvement across studies [3,14,26,27]. Changes in symptoms such as pain have been reported to remain

Table 2. Balance diagnostics for baseline (pretransplantation) characteristics of pre- and post-transplantation patients before and after propensity-score matching. Data are *n* (%) unless otherwise stated.

		Unmatched characteristics			Propensity-score matched characteristics		
Baseline characteristics		Pretransplantation (*n* = 99)	Post-transplantation (*n* = 274)	aSMD	Pretransplantation (*n* = 99)	Post-transplantation (*n* = 274)	aSMD
Age (years)	Mean	54.7	56.3	0.129	53.9	56.3	0.194
Sex	Male	65 (65.7)	148 (54.0)	0.242	55 (55.6)	148 (54.0)	0.024
	Female	34 (34.3)	126 (46.0)		44 (44.4)	126 (46.0)	
Ethnicity	White	93 (93.9)	257 (93.8)	0.011	93 (93.9)	257 (93.8)	0.011
	Other	6 (6.1)	17 (6.2)		6 (6.1)	17 (6.2)	
BMI (kg/m^2)	Mean (SD)	28.5	27.2	0.270	26.9	27.2	0.061
Blood group	O	62 (62.6)	141 (51.5)	0.196	45 (45.5)	141 (51.5)	0.167
	Non-O	37 (37.4)	133 (48.5)		54 (54.5)	133 (48.5)	
HCC status	Yes	27 (27.3)	58 (21.2)	0.166	19 (19.2)	58 (21.2)	0.032
	No	72 (72.7)	216 (78.8)		80 (80.8)	216 (78.8)	
MELD score	<10	22 (22.2)	28 (10.2)	0.506	10 (10.1)	28 (10.2)	0.195
	10–15	29 (29.3)	61 (22.3)		20 (20.2)	61 (22.3)	
	15–20	22 (22.2)	57 (20.8)		21 (21.2)	57 (20.8)	
	>20	26 (26.3)	128 (46.7)		48 (48.5)	128 (46.7)	
Primary liver disease	Other *	24 (24.2)	77 (28.1)	0.194	31 (31.3)	77 (28.1)	0.201
	Alcoholic	26 (26.3)	67 (24.5)		29 (29.3)	67 (24.5)	
	Cholestatic	19 (19.2)	57 (20.8)		18 (18.2)	57 (20.8)	
	NAFLD	16 (16.2)	30 (10.9)		10 (10.1)	30 (10.9)	
	Viral	14 (14.1)	43 (15.7)		11 (11.1)	43 (15.7)	

aSMD, absolute standardized mean difference; BMI, body mass index; MELD, model of end-stage liver disease; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.

*See full list of included conditions in Table S1.

Table 3. Overall and domain-specific health-related quality of life for pre- and post-transplantation patients in the unmatched and propensity-score matched samples, and the estimated average treatment effect (ATE) attributable to transplantation on health-related quality of life.

	Pretransplantation group		Post-transplantation group		
	Unmatched score (95% CI)	Propensity-matched score (95% CI) *	Unmatched score (95% CI)	Propensity-matched score (95% CI) *	Average treatment effect (95% CI) *
Overall score	66.0 (62.5–69.4)	64.8 (55.9–73.2)	79.3 (77.8–80.7)	83.7 (79.3–88.3)	6.3 (2.1–10.9)
Symptoms	65.2 (60.5–69.9)	64.1 (52.5–75.7)	77.2 (75.2–79.2)	82.0 (75.8–88.1)	6.3 (1.4–11.4)
Lifestyle effects	66.1 (61.0–71.2)	66.9 (54.7–80.2)	81.9 (79.7–84.1)	89.0 (82.1–96.2)	7.3 (1.7–13.4)
Cognition	72.9 (68.3–77.4)	76.1 (65.0–88.4)	80.7 (78.7–82.7)	85.6 (79.3–91.7)	3.3 (−0.6 to 7.4)
Distress	52.5 (47.4–57.5)	52.4 (39.4–65.6)	81.9 (79.3–84.4)	89.2 (81.7–96.5)	14.0 (4.8–23.8)
Sexual function	60.1 (53.3–67.0)	49.4 (31.6–66.8)	77.1 (73.5–80.7)	86.3 (74.4–97.9)	8.6 (3.1–15.0)
Quality of sleep	58.5 (54.4–62.6)	56.6 (46.5–66.3)	65.8 (63.9–67.7)	67.6 (61.8–73.8)	3.1 (0.2–6.3)
Loneliness	78.3 (74.5–82.1)	75.5 (67.3–84.7)	85.9 (84.2–87.7)	88.0 (82.9–93.9)	3.5 (0.5–6.7)
Hopelessness	64.6 (60.8–68.4)	62.7 (53.3–71.8)	76.3 (74.2–78.4)	77.0 (70.8–83.8)	5.9 (1.4–10.6)
Social stigma	73.9 (69.2–78.5)	78.5 (67.5–89.2)	86.5 (84.6–88.4)	92.4 (86.8–97.9)	5.9 (1.6–10.6)

*Calculated by incorporating known predictors of HR-QoL (age; sex; ethnicity; blood group; BMI; pretransplantation MELD score; hepatocellular carcinoma status), and incorporating patients who were directly matched based on pre- and post-transplantation questionnaire completion. In this context, the average treatment effect (ATE) is the estimated mean effect on the HR-QoL of the whole sample being transplanted (e.g. equivalent to the quantity of interest in a randomized control trial) (22).

Figure 2 Radar plots of overall health-related quality of life and in each SF-LDQOL domain in pre- (green) and post-transplantation (red) patients. Solid lines represent mean values, shaded areas represent 95% confidence intervals. b. Propensity-score matched pre- and post-transplantation patients. Abbreviations: D1 = Domain 1 (symptoms of liver disease), D2 = Domain 2 (effects of liver disease), D3 = Domain 3 (concentration/memory), D4 = Domain 4 (health-related distress), D5 = Domain 5 (sexual function), D6 = Domain 6 (quality of sleep), D7 = Domain 7 (loneliness), D8 = Domain 8 (hopelessness), D9 = Domain 9 (stigma of liver disease), O = Overall score.

nonsignificant in some cases [26], whereas there was a significant improvement observed in the symptoms domain of the SF-LDQOL in this sample (ATE: 6.3, 95% CI 1.4–11.4).

In contrast, the evidence for improvement in psychosocial health is less conclusive with some reports of

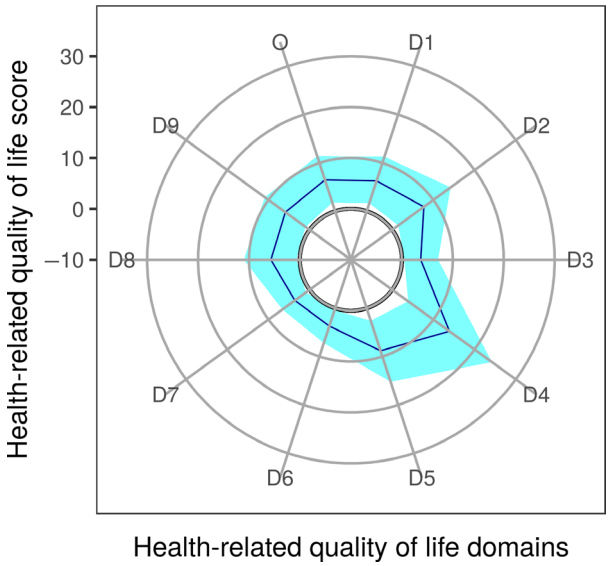

Figure 3 Radar plot of the average Treatment Effect (ATE) attributable to transplantation overall and in each SF-LDQOL domain. Solid lines represent mean values, shaded areas represent 95% confidence intervals. Abbreviations: D1 = Domain 1 (symptoms of liver disease), D2 = Domain 2 (effects of liver disease), D3 = Domain 3 (concentration/memory), D4 = Domain 4 (health-related distress), D5 = Domain 5 (sexual function), D6 = Domain 6 (quality of sleep), D7 = Domain 7 (loneliness), D8 = Domain 8 (hopelessness), D9 = Domain 9 (stigma of liver disease), O = Overall score.

no change [26–28] or slight improvement [3,14] in various domains being assessed. Nevertheless, psychosocial function has still been reported to be satisfactory in long-term follow-up studies [14]. Our results indicate there were significant improvements in most aspects psychosocial health assessed. However, cognitive function was not found to demonstrate a significant change in this cohort attributable to transplantation (ATE: 3.3, 95% CI: −0.6 to 7.4). Pretransplantation counselling process should reflect this, as well as potential disparities in improvements (particularly in quality of sleep, loneliness and social stigma), and that statistically significant improvements may not reflect clinical improvement from a patient perspective. Sexual function is also known to be a potential issue pre- and post-transplantation for both men and women [29]. While there is some evidence to support improvement after transplantation, this is not conclusive and may be influenced by a reluctance to discuss the topic openly [3]. This was observed within this cohort, with three items being excluded because of levels of missingness > 20%. Therefore, while these results supported an overall improvement in sexual function, this does not represent a comprehensive assessment of this aspect of health and may be subject to volunteer bias. Overall, more research is required to further understand the determinants of each health domain and identify specific avenues for improvement.

Quality of life following transplantation is multifactorial and has the potential to be influenced by recipient-, donor- and organ-related factors, as well as the time-point at which it is measured. In the mixed-effects linear regression model, transplantation in non-HCC patients was associated with a significant increase in overall HR-QoL, but with no change in patients with HCC (Table 1). This may be expected given that pretransplantation patients with HCC have a significantly higher overall HR-QoL than pretransplantation patients without HCC. Moreover, no significant difference in HR-QoL between HCC and non-HCC groups is seen following transplantation. These results make intuitive sense: many pretransplantation patients with HCC do not have established liver failure and may have minimal or no physical symptoms. The impact of the diagnosis of cancer on psychosocial wellbeing is well described and may also influence HR-QoL in HCC patients. While the full impact a diagnosis of HCC has on the HR-QoL in these patients may not have been captured, it is important to highlight in counselling that they may not experience a significant improvement in terms of liver disease-specific HR-QoL. In contrast, within the mixed-effects model (Table 2) there were no significant differences in overall HR-QoL observed between the different aetiologies of primary liver disease. While patients with end-stage liver disease undoubtedly have lower HR-QoL than those without, these results remain consistent with the current balance of evidence [14,30–33].

There were no significant differences observed between the re-transplantation status and time since transplantation post-transplantation subgroups in regard to overall quality of life (Table 1). While perhaps contrary to expectations, these results are reflected in other studies which indicate that the overall HR-QoL after adjustment tends to remain stable over time after the first year post-transplantation [13–16,34], and that re-transplantation does not appear to significantly affect long-term QOL [15,17]. In contrast, patients who received a DCD-organ were estimated to have a significantly worse HR-QoL ($\beta = -4.61$, 95% CI: −8.95 to −0.24, $P = 0.043$) compared to those who received a DBD-organ. This is consistent with other work on this topic [18,19], and may reflect the increased risk of morbidity in DCD-organ recipients [35–37]. However, it should be noted there is some

evidence to suggest that clinical outcomes can be equivalent with appropriate patient selection [38,39], and a recent study of long-term DCD-recipients has demonstrated no difference in HR-QoL between these groups [40]. While the finding of a lower HR-QoL in DCD-organ recipients has important implications for advising patients being offered these organs, it should be emphasized that this does not negate the benefits of higher quality-adjusted life years gained from accepting a DCD transplantation [20].

Although widely used, generic HR-QoL instruments (such as SF-36) often fail to capture important physical, psychological, emotional and/or social aspects which may affect the quality of life of pretransplantation patients, such as social stigma [41]. While there have been several different instruments developed to assess HR-QoL liver transplantation patients, there remains no gold-standard [8,14]. The psychometric properties of the SF-LDQOL questionnaire have been evaluated previously [9], and it was selected for its disease-specific aspects, correlation with SF-36 and clinical utility. An excellent initial response rate (80%) was obtained, which compares favourably to other HR-QoL studies in this population [13,14,19,42], therefore volunteer and selection biases were minimized. However, because of the cross-sectional nature of this study there are several factors that may have influenced the HR-QoL results observed. Frequent clinic attendees were more likely to have been encountered, and so may have had worse HR-QoL because of higher MELD scores; shorter postoperative periods; or higher rates and/or severities of complications. In contrast, those with the worst HR-QoL may have died or been (re-) transplanted which introduces the risk of survival bias and overestimation of HR-QoL in the cohort.

This was a single-centre study, and so it is important to recognize the impact of patient experience and non-health-related factors can have on patient-reported outcome measures [43]. As these could differ between the transplantation units, the results reported may not reflect the experiences of patients in other areas. In ideal circumstances, these concerns could be addressed through a prospective, multi-centre longitudinal study in which a liver disease-specific questionnaire is administered to patients both pre- and post-transplantation. The ultimate aim should be to embed quality of life assessment within routine practice in transplantation, which would be in line with the drive towards more patient-centred healthcare in the NHS [43,44]. Moreover, this could provide valuable clinical information given there is evidence to suggest that quality of life can be predictive of survival [45,46] and hospitalization [47] in pretransplantation patients.

One of the primary advantages of using a propensity-score matched analysis in this study is that the waiting list process for transplantation is inherently selective. Therefore, comparing the change in quality of life in those who have been transplanted alone cannot provide an unbiased assessment of the effect of liver transplantation. Furthermore, while propensity-score matching is not, and should not be, a substitute for randomized controlled trials, its use can allow causal inference in the context of observational research where a trial is not possible. However, unlike randomization, it does not account for unobserved covariates which might affect quality of life, such as those related to pretransplantation (e.g. duration on the waiting list, pre-existent mental health disorders) or post-transplantation status (e.g. immunosuppressive medications, chronic graft failure) [3]. Nevertheless, without the option to randomize patients to receipt of a liver transplantation (because of pragmatic and ethical considerations), propensity-score matching provides the best method of causal inference regarding the effect of transplantation upon HR-QoL. Finally, there is also no comparison made to healthy controls to determine whether HR-QoL also returns to "baseline", and previous work suggests that quality of life does remain lower than the general population [26,48,49]. Therefore, patient counselling must continue to ensure expectations regarding post-transplantation health remain realistic [48].

Conclusion

In conclusion, there is a significant improvement in health-related quality of life in patients undergoing liver transplantation. This was also observed across all quality of life domains, bar cognitive function. However, patients with HCC did not exhibit a significant increase in overall HR-QoL associated with transplantation. Furthermore, the quality of life observed in post-transplantation patients remained consistent according re-transplantation status, and time since transplantation. In contrast, patients who received a DCD-organ were estimated to have a significantly lower HR-QoL compared to those who received a DBD-organ. These findings may assist in counselling pretransplantation patients on their expected quality of life post-transplantation. However, more research is required to further understand the determinants of

each health domain and identify avenues for further improvement.

Authorship

KAM, EMH and RO designed the study. KAM, AS and JC collected data. KAM, TMD and EMH analysed data, and all the authors contributed to writing this paper.

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Conflict of interest

None.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Primary liver disease of pre- and post-transplantation patients in the cohort.

Table S2. Overall and domain-specific treatment effects attributable to transplantation within the cohort.

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