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Factors Affecting Quality of Life in Liver Transplant Candidates: An Observational Study

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Abstract: Health-related quality of life (HRQOL) before and after liver transplant (LT) is an important outcome in LT candidates as, in these patients, HRQOL is commonly impaired. However, evidence regarding factors that influence HRQOL in patients with end-stage liver disease is inconclusive. The aim of the present study was to identify factors associated with poor HRQOL. An observational study was conducted over LT candidates. The 36-item Short Form Health Survey (widely used to assess HRQOL) and the Hospital Anxiety and Depression Scale were administered to 211 patients during the pre-transplant assessment. Baseline demographic and clinical data were also collected. Multiple regression analysis was performed to investigate risk factors for poor HRQOL. Female sex (lower B = 7.99 95%C = 0.07–15.92, higher B = 18.09 95%CI = 7.56–28.62), encephalopathy (lower B = −9.45, 95%CI = −14.59–−4.31, higher B = −6.69, 95%CI = −13.13 to −0.25), higher MELD scores (lower B = −1.14, 95%CI = −1.67 to −0.61, higher B = −0.33, 95%CI = −0.65 to −0.12), anxiety (lower B = −3.04 95%C = −4.71 to −1.36, higher B = −1.93 95%CI = −3.39 to −0.47)and depression (lower B = −3.27 95%C = −4.46 to −2.08, higher B = −1.02 95%CI = −1.90 to −0.13) symptoms were associated to poorer HRQOL. Psychosocial interventions should be addressed to liver transplant candidates, especially to women, patients with anxiety, depression or episodes of encephalopathy, in order to prevent the impact that these conditions can have on HRQOL.

Keywords: liver transplant; quality of life; anxiety; depression; psychosocial factors

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1. Introduction

Liver transplantation (LT) is sometimes the only treatment for patients with end-stage liver disease (ESLD). The shortage of available organs for transplantation makes it necessary to evaluate and select candidates to guarantee an optimal graft and recipient survival [1,2]. As survival rates have improved [3], more attention is devoted to quality of life before and after transplantation [4] as it is an important outcome from patient's perspective.

The concept of health-related quality of life (HRQOL) includes those aspects of quality of life that affect physical or mental health, and is defined as "an individual's or group's perceived physical and mental health over time" [5]. HRQOL consists of three components: psychological, social, and physical functioning, and it is measured by means of standardized, self-administered questionnaires [6]. Research concerning patients with ESLD show impaired HRQOL compared to normal population [7], and to patients with chronic liver disease [8], having this illness an impact in the majority of HRQOL domains [9].

Evidence about the factors that influence pre-transplant HRQOL in ESLD patients is inconclusive. Hepatic encephalopathy has been found to be the strongest independent predictor of poor HRQOL [10]. While ascites or encephalopathy were predictive of HRQOL scores, mixed evidence has been found for the Model of End-Stage Liver Disease (MELD), a predictor of mortality in patients with ESLD. Some studies found no association of MELD with HRQOL [11,12], even finding poor HRQOL in patients with low MELD scores, whereas other studies found a significant correlation between MELD scores and HRQOL [10,13,14].

Some studies found no effects on HRQOL due to disease etiology [7,9]. However, others report that alcohol and viral cirrhosis etiologies had poorer HRQOL than hepatocellular carcinoma or cholestatic disease [15], or that non-alcoholic fatty liver disease showed lower SF-36 scores than other etiologies [16].

Some sociodemographic factors associated to impaired HRQOL in cirrhotic patients were younger age [9] and female sex [16,17]. Conversely, another study found that older patients were more affected in all HRQOL domains [16]. Level of education seems to affect HRQOL and may partially explain gender differences. When controlling for education, differences in HRQOL disappeared among the lesser educated group, while male patients with more than 12 years of education showed higher HRQOL [18].

Psychological distress associated with the transplant can impact HRQOL. Candidates for LT with higher scores in depression [19], anxiety, and trauma [20], showed lower scores in all SF-36 domains. Furthermore, an ineffectively treated depression in the pre-transplant period has been associated to worst long-term survival [21,22], and lower post-LT quality of life [23]. The presence of mood disorder, lack of social support, and alcohol and substance misuse before transplantation were associated to mental and physical morbidity after transplantation [24], with alcohol-related liver disease being the second most common indication for LT [25].

Research on factors associated with HRQOL is scarce and more evidence is needed. We present this study with the aim of identifying risk factors associated with lower HRQOL in liver transplant candidates.

2. Methods

2.1. Study Design and Setting

An observational study was performed with a sample of patients assessed as LT candidates to identify risk factors affecting HRQOL. Information about patient's status (death or alive) and about their transplantation status (if they had undergone transplantation) on 1st June 2020 was obtained from hospital's clinical records and double checked against the Catalan public health shared system register.

Participants were recruited from May 2017 to March 2020, in Hospital Clinic of Barcelona, one of the three tertiary care centers conducting LT in a broad area that includes all Catalonia, Balearic Islands and Andorra. Transplant candidates who agreed to participate, attended a visit before LT in which sociodemographic and clinical variables were gathered and questionnaires were completed.

2.2. Participants

All consecutive adult patients assessed by liver specialist as candidates for LT were referred to a psychological visit to check for eligibility for the study. When a patient was diagnosed with alcohol-related liver disease or the presence of a substance use disorder was suspected, they were referred to addiction treatment and had to provide urine samples weekly to check abstinence from alcohol and drugs. Those who refused to attend addiction treatment, or did not achieve abstinence, were excluded from the study. Those who had impaired cognitive functioning as per a Mini-Mental State Examination (MMSE) score below 22 were also excluded. Those candidates with encephalopathy or with a MMSE score between 22 and 27, completed the evaluation with the help of a caregiver. Of the 242 LT candidates derived to psychological assessment, 24 patients were not included (Figure 1),

and 218 candidates provided informed consent. Finally, SF-36 and The Hospital Anxiety and Depression Scale (HADS) questionnaires were fully completed by 211 candidates.

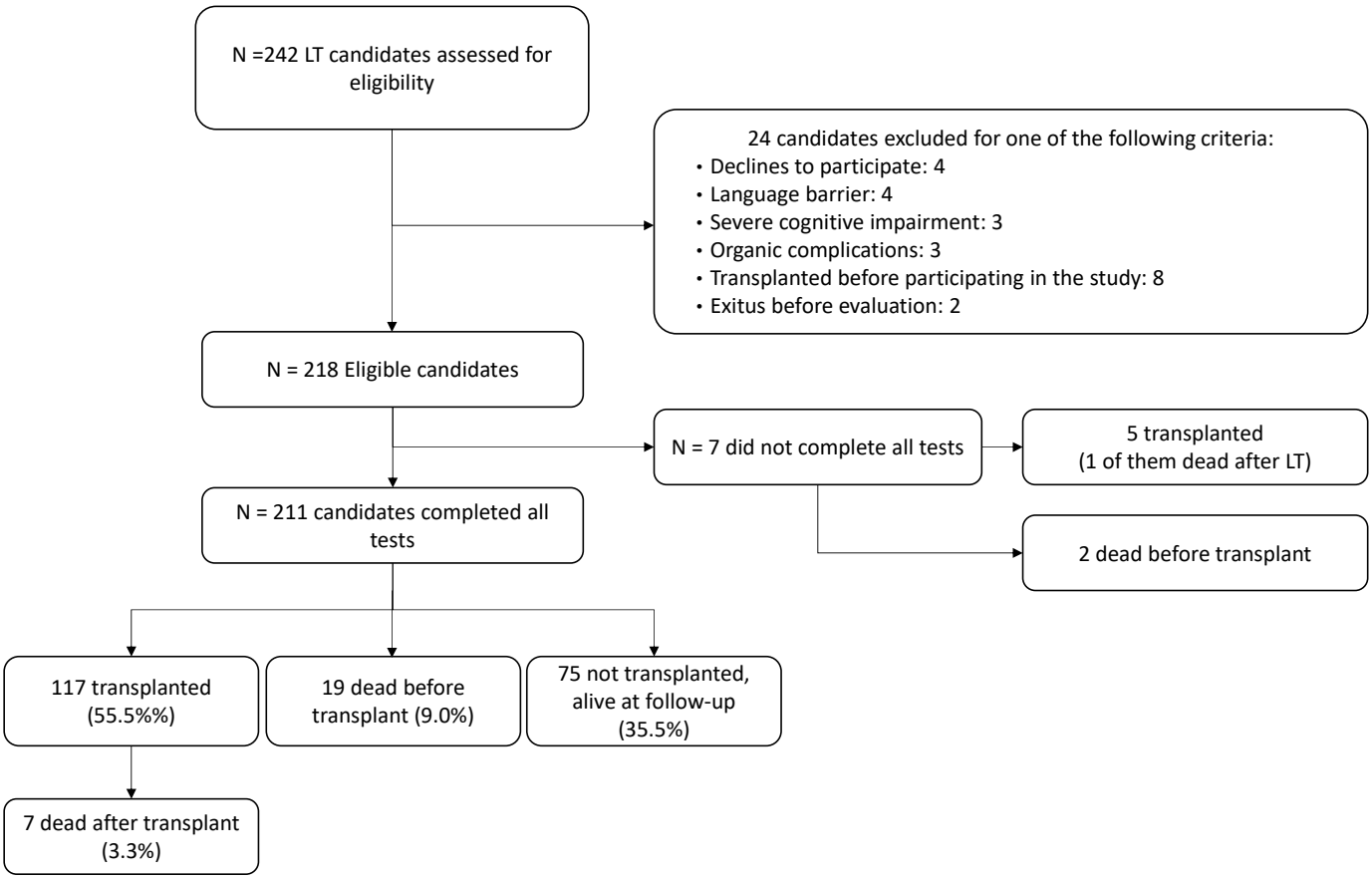

Figure 1. Flowchart of recruitment and exclusion of liver transplant candidates.

2.3. Baseline Sociodemographic and Clinical Variables

Variables included in the analysis as risk factors for HRQOL were: age, gender, etiology of cirrhosis (alcohol-related liver disease with or without viral hepatitis C versus other etiologies including viral hepatitis, autoimmune hepatitis, NASH, congenital hepatorenal polycystic disease, cryptogenic liver disease or hepatocellular carcinoma), level of education, civil status, presence of at least one episode of encephalopathy, MELD score, status at 1st June 2020 (alive or death), and presence of anxiety and depression measured by HADS score ≥ 8. These variables were obtained during the clinical interview and from the patient's clinical records, using the latest available MELD score. The MELD is an index considered a good predictor of three-month survival in cirrhotic patients of any etiology and, although it has some limitations, it is usually used as a waiting list priority allocation system [26].

The 36-item Short Form Health Survey (SF-36) is one of the most commonly used generic questionnaires to assess HRQOL [27]. The SF-36 Spanish version was used [28]. It evaluates aspects of HRQOL in eight domains: Physical Functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning, Role Emotional and Mental Health. Raw SF-36 scores are transformed to a range of 0–100, with 0 being the worst possible perceived HRQOL and 100 the best possible score. The SF-36 showed good reliability, with a Cronbach's alpha higher than 0.7 for all scales, good discrimination among severity groups and high correlations with other HRQOL instruments. Questionnaire scores predicted mortality and were able to detect improvement due to therapeutic interventions in several diseases [29].

The Hospital Anxiety and Depression Scale (HADS) Spanish version was used [30]. It is a 14-item self-report screening scale developed to indicate the possible presence of anxiety and depression in medical non-psychiatric settings. HADS Anxiety (HADS-A) and Depression (HADS-D) subscales have seven items each, scored on a four-point Likert scale from 0 to 3. A score between 0 and 7 in a subscale is considered as being in the normal range, and a score of 8 or higher suggests the presence of mood or anxiety [31]. The HADS showed good internal consistency (with a Cronbach's Alpha of 0.9 for the complete scale, and 0.84 and 0.85 for the depression and anxiety subscales respectively), external validity, and good sensitivity (72%) and specificity (87%) in identifying cases of psychiatric disorder [30].

The questionnaires were self-administered during the pre-transplant assessment.

2.4. Ethical Considerations

All candidates were included after signing an informed consent approved by the Hospital Clinic Ethical Committee (HCB/2016/0708, September 2016), were informed that their participation was voluntary and that refusal to participate or discontinue participation at any time would not involve changes in treatment or loss of benefits. The study was performed according to the Helsinki Declaration (Fortaleza, Brazil, October 2013), and the Spanish national regulations of biomedical research (Ley 14/2007).

2.5. Statistical Methods

SPSS 20.0 (IBM, Armonk, NY, USA) was used for data analysis. Data were checked for normal distribution using the Kolmogorov-Smirnov test. Since variables did not follow a normal distribution, and significant skewness was detected in some scales, non-parametric tests were used. Kruskal–Wallis and Mann–Whitney U tests were used to analyze statistical differences on SF-36 domains according to sociodemographic and clinical variables. A p value of <0.05 was considered statistically significant. Continuous variables were categorized as follows: Age ($\leq$60 vs. $\geq$60 years), MELD score (<19 vs. $\geq$19) and HADS score (<8 vs. $\geq$8). A multiple regression analysis was performed to identify independent risk factors for lower scores on SF-36 domains.

3. Results

A total of 211 participants with median age of 59.7 (IQR, 54.5–63.5 years) and 157 male patients (74.4%) were assessed. Of them, 117 (55.5%) had undergone LT, 19 (9.0%) died before LT, and 75 (35.5%) were alive and had not undergone transplantation at Hospital Clinic by 1st June 2020 (Figure 1). Of those who were not transplanted by June 1st, 23 were on stand-by (not active on waiting list) because of illness improvement, and 17 were removed or on stand-by from waiting list for contraindications (14 patients had medical contraindications, one patient had an alcohol relapse, one patient was non-adherent to medical appointments and one patient was ambivalent whether to undergo transplantation or not and had not been included in the waiting list yet). One patient was transplanted at another Spanish hospital whose waiting list was shorter and a total of 34 patients were on the waiting list for transplantation.

Alcohol-related liver disease with or without viral hepatitis C was present in 65.4% of the sample and the rest had other etiologies (34.6%). The most common etiologies other than alcohol were viral hepatitis (20 patients had non-alcohol related viral hepatitis C and four patients had non-alcohol related viral hepatitis B etiology), autoimmune hepatitis in 12 patients, NASH in 12 patients and congenital hepato-renal polycystic disease in 6 patients. Hepatocellular carcinoma as primary diagnosis for transplantation alcohol or non-alcohol related, was present in 47 patients. Median MELD score was 17.5 (RIQ 14–20). A total of 33 patients had a substance use disorder other than alcohol. Psychiatric comorbidities were present in 71 patients, some of whom had more than one diagnosis. The most prevalent psychiatric diagnosis was major depressive disorder, present in 62 patients, 45 of them having suffered from depression at some point in the past but not at the time

of evaluation, and 17 of them with a current diagnosis of depression. Other psychiatric diagnoses found in the sample were anxiety disorder in 12 patients (six with generalized anxiety disorder, five with panic disorder, and one with agoraphobia), antisocial personality disorder in three patients, eating disorder in one patient, and a well-controlled psychotic disorder in one patient. Median time from assessment and actual liver transplantation was 68 days (RIQ 22–182).

Table 1 shows sociodemographic and clinical characteristics with median comparisons and interquartile ranges for the total sample and each SF-36 domain. Statistically significant differences were observed on some SF-36 domains with lower scores for female patients, candidates with any episode encephalopathy, those with MELD score $\geq$19, HADS scores $\geq$8 and patients who were dead by 1st June 2020. Patients transplanted primarily due to hepatocellular carcinoma had significantly higher scores in all SF-36 domains.

Multivariate regression analysis was performed to assess risk factors affecting SF-36 scores (Tables 2 and 3). HADS-D score was an independent risk factor for reduced scores in all domains of SF-36 (lower B = −3.27 95%C = −4.46 to −2.08, higher B = −1.02 95%CI = −1.90 to −0.13), and HADS-A score for reduced scores in Bodily Pain (B = −1.93, 95%CI = −3.39 to −0.47), Role Emotional (B = −3.04, 95%CI = −4.71 to −1.36) and Mental Health (B = −2.65, 95%CI = −3.39 to −1.90). Regarding other baseline variables, female sex was independently associated with lower Physical Functioning (B = 14.56, 95%CI = 6.75–22.34), Role Physical (B = 13.66, 95%CI = 0.80–26.51), Social Functioning (B = 7.99, 95%CI = 0.07–15.92) and Role Emotional (B = 18.09, 95%CI = 7.56–28.62) scores. Having suffered at least one episode of encephalopathy was independently associated with lower Physical Functioning (B = −9.16, 95%CI = −15.96 to −2.36), General Health (B = −9.45, 95%CI = −14.59–−4.31) and Vitality (B = −6.69, 95%CI = −13.13 to −0.25). MELD score was independently and inversely associated with Physical Functioning (B = −1.04, 95%CI = −1.57 to −0.52), Role Physical (B = −1.00, 95%CI = −1.87 to −0.14), Social Functioning (B = −1.14, 95%CI = −1.67–−0.61) and Mental Health (B = −0.33, 95%CI = −0.65 to −0.12) scores. Having a high-school level of education was associated with better functioning on Role Physical domain (B = 14.86, 95%CI = 1.59–28.13). All other variables did not show significances in the multiple regression analysis (all *p*-values >0.05).

Table 1. Differences on the SF-36 domains according to baseline sociodemographic and clinical variables.

	N (%)	Physical Functioning	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health
Totals (Median, RIQ)	211	60 (30–85)	25 (0–100)	70 (45–100)	40 (30–50)	50 (30–70)	80 (55–100)	100 (66.7–100)	80 (60–92)
Age									
≤60	115 (54.5%)	65 (32.5–90)	25 (0–100)	70 (45–100)	40 (30–50)	50 (27.5–70)	80 (51.3–100)	100 (66.7–100)	80 (60–90)
>60	96 (45.5%)	55 (30–81.3)	37.5 (0–100)	72.5 (45–100)	35 (25–50)	50 (30–75)	80 (55–100)	100 (100–100)	82 (60–92)
Gender									
Female	54 (25.6%)	45 (17.5–75)	0 (0–75)	57.5 (32.5–79.4)	35 (21.3–48.8)	47.5 (30–63.8)	67.5 (35.6–100)	100 (0–100)	74 (56–87)
Male	157 (74.4%)	65 (35–90) †	50 (0–100) †	77.5 (45–100) †	40 (30–50)	50 (30–80)	87.5 (60–100) *	100 (100–100) ‡	84 (64–92) *
Cirrhosis etiology									
Alcohol-related liver disease	138 (65.4%)	55 (25–85)	50 (0–100)	77.5 (45–100)	40 (30–50)	50 (30–73.75)	80 (55–100)	100 (100–100)	80 (64–95)
Others	73 (34.6%)	65 (35–85)	25 (0–100)	67.5 (35–90)	40 (30–50)	50 (25–65)	77.5 (42.5–100)	100 (66.7–100)	76 (56–88)
Primary diagnosis for tx									
Hepatocellular carcinoma	47 (22.3%)	85 (57.5–95) ‡	100 (37.5–100) ‡	90 (67.5–100) ‡	50 (40–65) ‡	65 (50–80) ‡	100 (80–100)‡	100 (100–100) ‡	88 (80–96) ‡
Others	164 (77.7%)	50 (25–81.3)	25 (0–100)	67.5 (40.6–90)	35 (25–45)	45 (20–65)	76.3 (41.3–100)	100 (66.7–100)	74 (52–88)
Level of education									
Primary education or less	41 (19.4%)	50 (35–80)	0 (0–75)	67.5 (32.5–90)	40 (30–50)	50 (20–60)	77.5 (47.5–100)	100 (66.7–100)	72 (52–92)
Secondary education	57 (27.0%)	60 (25–90)	25 (0–100)	77.5 (47.5–100)	35 (25–50)	50 (20–80)	77.5 (65–100)	100 (66.7–100)	80 (60–92)
High school diploma	82 (38.9%)	65 (31.3–85)	50 (0–100)	77.5 (45–100)	40 (26.3–55)	50 (31.3–73.8)	87.5 (51.3–100)	100 (100–100)	82 (64–92)
University or beyond	31 (14.7%)	65 (40–85)	50 (0–75)	67.5 (40–80)	35 (30–45)	45 (27.5–65)	80 (51.3–100)	100 (83.3–100)	76 (64–92)
Civil status									
Single	10 (4.7%)	72.5 (37.5–93.8)	0 (0–87.5)	85 (31.3–100)	40 (23.8–76.3)	50 (33.8–68.8)	82.5 (33.1–100)	100 (75–100)	84 (71–97)
Married	149 (70.6%)	60 (35–85)	25 (0–100)	70 (45–100)	40 (30–50)	50 (30–70)	80 (55–100)	100 (100–100)	80 (60–92)
Divorced	43 (20.4%)	55 (25–72.5)	50 (0–100)	67.5 (45–100)	35 (20–52.5)	50 (27.5–65)	77.5 (35–100)	100 (33.3–100)	80 (54–92)
Widowed	9 (4.3%)	75 (30–85)	50 (0–100)	67.5 (45–87.5)	25 (15–45)	55 (25–70)	90 (80–100)	100 (66.7–100)	84 (60–100)
Encephalopathy									
No	97 (46.0%)	75 (50–95)	50 (0–100)	77.5 (45–100)	45 (35–60)	55 (40–80)	90 (67.5–100)	100 (100–100)	84 (64–92)
Yes	114 (54.0%)	45 (25–75) ‡	25 (0–93.8)	67.5 (43.1–97.5)	35 (21.3–45) ‡	45 (20–60) ‡	76.3 (35.6–100) †	100 (66.7–100)	76 (56–92) *
MELD									
<19	136 (64.5%)	75 (40–90)	50 (0–100)	77.5 (47.0–90)	40 (30–55)	55 (35–80)	90 (67.5–100)	100 (100–100)	84 (68–93)
≥19	75 (35.5%)	45 (20–65) †	0 (0–87.5) †	67.5 (32.5–100)	35 (25–45)	40 (17.5–55) ‡	65 (30–90) ‡	100 (50–100) *	68 (48–88) ‡
HADS-Anxiety									
<8	173 (82.0%)	70 (45–90)	50 (0–100)	77.5 (55–100)	40 (30–55)	55 (35–80)	90 (67.5–100)	100 (100–100)	84 (68–96)
≥8	38 (18.0%)	25 (15–38.8) ‡	0 (0–25) ‡	43.8 (20.6–61.3) ‡	30 (15–35) ‡	25 (15–40) ‡	42.5 (15–66.9) ‡	50 (0–100) ‡	44 (37–62) ‡
HADS-Depression									
<8	174 (82.5%)	70 (45–90)	50 (0–100)	77.5 (55–100)	40 (30–53.8)	55 (40–80)	90 (65.6–100)	100 (100–100)	84 (68–95)
≥8	37 (17.5%)	25 (15–40) ‡	0 (0–0) ‡	45 (10–62.5) ‡	25 (15–30) ‡	20 (5–30) ‡	35 (12.5–67.5) ‡	33.33 (0–100) ‡	44 (36–56) ‡
Status									
Alive before LT	192 (91.0%)	65 (33.8–85)	37.5 (0–100)	68.8 (45–100)	40 (28.8–50)	50 (30–70)	83.8 (55–100)	100 (100–100)	80 (60–92)
Death before LT	19 (9.0%)	35 (17.5–46.5) †	25 (0–50)	77.5 (38.8–100)	35 (30–55)	45 (20–57.5)	60 (22.5–80) †	100 (66.7–100)	68 (48–86)

Mann-Whitney: Age, Gender, Cirrhosis etiology, Encephalopathy, MELD, HADS-A, HADS-D, Status. Kruskal-Wallis: Level of education and civil status. Data are presented as either n (%) or median (IQR). * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$.

Table 2. Factors associated with scores on SF-36 domains. Multivariate regression analysis.

	Physical Functioning		Role Physical		Bodily Pain		General Health		Vitality		Social Functioning		Role Emotional		Mental Health	
R-squared, *p*	0.458	0.00 *	0.293	0.00 *	0.268	0.00 *	0.264	0.00 *	0.398	0.00 *	0.467	0.00 *	0.318	0.00 *	0.614	0.00 *
Constant	94.45		48.46		77.51		37.0		61.15		99.1		82.86		88.8	
	B	*p*	B	*p*	B	*p*	B	*p*	B	*p*	B	*p*	B	*p*	B	*p*
Age	−0.39	0.09	0.32	0.41	0.00	0.99	0.16	0.36	0.19	0.40	−0.03	0.89	0.00	0.99	0.11	0.43
Gender	14.56	0.00 *	13.66	0.04 *	9.00	0.05	3.56	0.24	3.21	0.39	7.99	0.04 *	18.09	0.00 *	2.27	0.34
Cirrhosis etiology	5.81	0.13	−1.01	0.87	0.51	0.91	0.31	0.91	−2.33	0.52	−0.59	0.88	−0.33	0.95	−3.65	0.12
Level of education																
Primary education	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Secondary education	5.29	0.28	3.78	0.64	0.83	0.88	2.6	0.48	3.09	0.50	2.75	0.58	5.25	0.42	2.67	0.36
High school diploma	3.79	0.36	14.86	0.03 *	0.45	0.93	3.49	0.26	3.48	0.37	−0.19	0.96	2.13	0.70	2.5	0.31
University or beyond	4.35	0.42	9.63	0.28	−5.95	0.35	−0.71	0.86	1.16	0.82	1.17	0.83	3.44	0.64	3.58	0.27
Civil status																
Single	8.60	0.31	−12.42	0.37	−0.01	1.00	11.73	0.07	2.57	0.75	−3.02	0.72	−0.37	0.97	2.31	0.65
Married	6.37	0.13	−5.73	0.40	−0.79	0.87	3.04	0.33	−1.55	0.69	7.48	0.08	6.67	0.23	0.39	0.88
Widowed	14.05	0.11	6.16	0.67	−1.3	0.90	−9.45	0.15	−1.88	0.82	13.83	0.12	5.6	0.63	2.75	0.60
Divorced	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Encephalopathy	−9.16	0.01 *	−0.03	1.00	−1.25	0.76	−9.45	0.00 *	−6.69	0.04 *	−3.04	0.39	0.36	0.94	0.19	0.93
MELD	−1.04	0.00 *	−1.00	0.02 *	−0.01	0.98	−0.08	0.69	−0.41	0.11	−1.14	0.00 *	−0.16	0.65	−0.33	0.04 *
HADS-Anxiety	−0.48	0.45	−1.59	0.13	−1.93	0.01 *	−0.66	0.17	−0.99	0.10	−1.12	0.08	−3.04	0.00 *	−2.65	0.00 *
HADS-Depression	−3.12	0.00 *	−3.26	0.00 *	−1.99	0.00 *	−1.02	0.02 *	−2.80	0.00 *	−3.27	0.00 *	−1.82	0.02 *	−1.70	0.00 *

* $p < 0.05$.

Table 3. Beta coefficients and 95% confidence intervals for multivariate regression analysis significant factors.

	Gender		High School Diploma		Encephalopathy		MELD		HADS-Anxiety		HADS-Depression	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Physical Functioning	14.56	6.75–22.34			−9.16	−15.96–−2.36	−1.04	−1.57–−0.52			−3.12	−4.3–−1.95
Role Physical	13.66	0.80–26.51	14.86	1.59–28.13			−1.00	−1.87–−0.14			−3.26	−5.19–−1.33
Bodily Pain									−1.93	−3.39–−0.47	−1.99	−3.37–−0.62
General Health					−9.45	−14.59–−4.31					−1.02	−1.90–−0.13
Vitality					−6.69	−13.13–−0.25					−2.80	−3.92–−1.69
Social Functioning	7.99	0.07–15.92					−1.14	−1.67–−0.61			−3.27	−4.46–−2.08
Role Emotional	18.09	7.56–28.62							−3.04	−4.71–−1.36	−1.82	−3.4–−0.24
Mental Health							−0.33	−0.65–−0.12	−2.65	−3.39–−1.90	−1.70	−2.41–−0.99

4. Discussion

This study identified that certain factors (female sex, having experienced at least one episode of encephalopathy, higher MELD score and higher anxiety and depression HADS scores) were associated with poorer HRQOL in different SF-36 domains. These results can be useful when planning interventions to improve patient's care by transplant teams. Patients transplanted primarily due to hepatocellular carcinoma had significantly higher scores in all SF-36 domains, probably because those patients have compensated cirrhosis with better HRQOL as compared to patients transplanted for decompensated cirrhosis.

The main causes of liver disease leading to transplantation are alcohol-related liver disease and hepatitis C viral cirrhosis, which occur more frequently in men. Along with anatomic and sociocultural reasons, this contribute to the fact that women are less frequently evaluated and allocated for organ transplantation [32]. Consistently with our findings, female patients have been reported to have lower Physical Functioning and Role Physical scores in previous studies [16,18]. We also found significantly more impairment in Social Functioning and Role Emotional domains in women. Our results suggest that women LT candidates tend to experience more limitations in physical activities due to their illness, and their physical health and emotional problems have a greater impact on their work, daily and social activities. Evidence [33] indicates that social roles may be an explanation for this gender difference in HRQOL, since women tend to occupy nurturing roles that impair their ability to self-care when they are sick. This is associated to more psychological distress, poorer mental health, and higher rates of morbidity.

Women's' differential needs are less studied and interventions in transplant programs do not focus on this vulnerable group, contributing to increase gender disparities. This issue should be a matter of concern in future research. Developing psychological interventions that incorporate gender perspective is, therefore, needed, as well as improving social and family support to overcome the deficits that arise due to gender disparities.

As in previous studies that point to the impact of encephalopathy on HRQOL [10,34,35], candidates with encephalopathy had more impairment across several HRQOL domains (Physical Functioning, General Health and Vitality). An association between higher MELD scores and lower HRQOL has been consistently reported [13,14]. Even the minimal form of hepatic encephalopathy, has been found to be associated with poor quality of life and multiple episodes are associated with poor neurological outcomes even after liver transplantation [36]. A higher cognitive reserve has been associated to a better ability to withstand the demands of the disease, which leads to a better HRQOL [37]. Therefore, HE treatment, and the neuropsychological assessment and rehabilitation of cognitive functions before and after LT are crucial in order to promote a positive impact in HRQOL, and patients with a lower cognitive reserve should receive earlier measures to improve HRQOL [37].

Similarly to our findings, the presence of anxiety and depression in transplant candidates has already been reported as a factor associated with worse HRQOL in SF-36 [20]. Thus, assessing and treating patients with anxiety or/and depression before and after the transplant could benefit, not only patients' HRQOL, but also improving overall long-term success of transplantation. Cognitive behavioral therapy, including anxiety reduction and pain management techniques, has been evaluated as being a beneficial approach with LT patients suffering from anxiety and depression [38].

Pre-transplant assessment should include the evaluation of the different components related to quality of life in order for the patients to undergo the transplant in a better health condition, to avoid health complications and improve post-transplant survival. Considering the impact that this chronic disease can have on physical, psychological, and social wellbeing, the treatment of quality of life of these patients should be considered as a crucial part of the intervention.

This study has several limitations. To start with, data were collected in a single center, which limits generalizability of the results. This is partially compensated because Hospital Clinic of Barcelona is one of the three tertiary hospitals conducting LT in a broad area that

covers a population of 10 million. A possible bias is that patients who were not able to stop using alcohol or drugs or rejected to participate in urine controls were excluded from the study. No differences were found in HRQOL between alcohol-related liver disease candidates that maintained abstinence and adhered to urine controls and candidates with other cirrhosis etiologies, although these results should not be generalized to all alcohol-related liver disease patients. Medical complications and comorbidities that may have an impact on HRQOL were not measured. No neuropsychological assessment was conducted to detect encephalopathy and information was obtained only from clinical history [39]. It would be interesting to compare pre and post-transplant data on HRQOL, anxiety and depression and this would be the matter of future research work.

This study has also strengths. It has been conducted with a sample from clinical practice candidates systematically assessed for LT. The sample assessed is large. Using widely adopted generic instruments, such as SF-36 and HADS, increases the possibility of comparing the scores of the patients with other transplant populations and healthy controls. Most of the existing studies on quality of life and liver transplantation are retrospective and evaluate quality of life after transplantation up to one or many years later. The present study places more emphasis on identifying the variables that should be considered by professionals before transplantation to help the patient arrive at the transplant in good physical and mental conditions and prevent possible complications. It also stresses the importance of assessing anxiety and depression before transplant. This paper builds upon previous findings [40] and shows the importance of considering gender as a risk factor for worse quality of life and suggests the convenience of more interventions in this group. Although Spain is one of the countries with higher number of liver transplants per million population, this is one of the few liver transplant studies conducted in Mediterranean countries. The Western European family model is characterized by co-residence, solidarity, and intergenerational relationships but with recent economic crisis state investment in social and health aids has been decreasing progressively, placing greater burden on women for caring for sick and elderly relatives [41]. When women face an illness, they have little space to take care of themselves. Investment is needed in health and social policies that relieve families, especially women, of their burden of care, to eliminate gender inequalities in health.

In conclusion, candidates with a lower HRQOL, especially women, with anxiety or depression or those experiencing encephalopathy episodes, and high MELD score, require more intensive psychosocial interventions before and after LT.

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Data Availability Statement: The data presented in this study are available from the corresponding author on reasonable request.

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