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Original Article

Health-related quality of life in patients with compensated and decompensated liver cirrhosis

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ABSTRACT

Background: Compensated (Child-Pugh [CP] A) and decompensated (CP B/C) liver cirrhosis significantly differs in terms of impairment of health-related quality of life (HRQoL). However, sufficient data on potentially treatable factors associated with HRQoL in both stages of the disease are still lacking. Consequently, aims of this study were to determine differences in HRQoL between patients with compensated and decompensated liver cirrhosis and to identify potentially treatable factors associated with HRQoL.

Methods: 218 patients with liver cirrhosis were enrolled into this study. Chronic Liver Disease Questionnaire (CLDQ) was used to assess HRQoL. Covert hepatic encephalopathy (CHE) was diagnosed according to a combination of Psychometric Hepatic Encephalopathy Score and Critical Flicker Frequency. Frailty was assessed by Clinical Frailty Scale (CFS).

Results: HRQoL differed between patients with CP A (n = 133) and CP B/C (n = 85) liver cirrhosis (CLDQ total score: 5.6 vs. 4.8, $p < 0.001$). Multivariate analysis identified a history of falls in the recent year, presence of CHE, female gender, active smoking, higher CFS, and higher serum levels of CRP as independent predictors of impaired HRQoL (all $p < 0.05$) in patients with CP A liver cirrhosis. In patients with CP B/C liver cirrhosis, female gender, a history of overt hepatic encephalopathy, and lower hemoglobin were independently associated with impaired HRQoL (all $p < 0.05$).

Conclusions: Predictors of impaired HRQoL differ in patients with CP A or CP B/C liver cirrhosis. Focusing on treatable factors in routine clinical practice may improve HRQoL in all stages of liver cirrhosis.

1. Introduction

Liver cirrhosis is a common cause for morbidity and mortality [1]. In 2010, more than one million deaths worldwide were attributable to end-stage liver cirrhosis representing a major burden of disease [2]. Liver cirrhosis can roughly be divided into two stages depending on the degree of decompensation. Decompensated liver cirrhosis (Child-Pugh [CP] B/C) is defined by the onset or presence of characteristic complications such as ascites, hepatic encephalopathy (HE), spontaneous bacterial peritonitis or variceal bleeding. All complications are associated with an exponential increase in mortality compared to the compensated stage of the disease (CP A) [3].

In recent years, patients reported outcomes came to the fore, and several studies have demonstrated that health-related quality of life (HRQoL) is impaired in patients with liver cirrhosis when compared to the healthy general population [4,5]. HRQoL is inversely correlated with the severity of underlying chronic liver disease [4,6] and studies were able to identify factors (e.g. ascites, decreased albumin, or covert hepatic encephalopathy (CHE)) associated with impaired HRQoL in those patients [7,8]. However, these studies looked at liver cirrhosis as one entity without a differentiation between the compensated (CP A) and decompensated (CP B/C) stage of the disease. A recent study by

Abbreviations: CFF, Critical Flicker Frequency; CFS, clinical frailty scale; CHE, covert hepatic encephalopathy; CLDQ, chronic liver disease questionnaire; HE, hepatic encephalopathy; HE1, hepatic encephalopathy grade 1; HRQoL, health-related quality of life; MHE, minimal hepatic encephalopathy; NAFLD, non-alcoholic fatty liver disease; OHE, overt hepatic encephalopathy; PHES, Portosystemic Hepatic Encephalopathy Score

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Tapper et al. was one of the first studies to identify determinants of impaired HRQoL in compensated patients (CP A) representing the majority of patients with liver cirrhosis in clinical practice [9]. Finally, predictors of impaired HRQoL in compensated and decompensated liver cirrhosis are not well characterized. Therefore, the aim of the present study was first to determine differences in HRQoL between patients with compensated (CP A) and decompensated (CP B/C) liver cirrhosis and second to identify potentially treatable factors associated with impaired HRQoL in both stages of the disease.

2. Patients and methods

2.1. Patients

311 in- and outpatients with liver cirrhosis were screened and finally 218 were prospectively enrolled into the present study between March 2017 and July 2018 at the Cirrhosis Center Mainz (CCM) of the University Medical Center of the Johannes Gutenberg-University in Mainz, Germany. The leading etiology of underlying liver disease was determined according to clinical, serological and histological findings. Diagnosis of liver cirrhosis was made by histology, typical appearance in ultrasound or radiological imaging, endoscopic features of portal hypertension, and medical history. Blood biochemistry (bilirubin, albumin, international normalized ration (INR), sodium, potassium, creatinine, c-reactive protein [CRP], white blood cell count, hemoglobin, and ammonia) was performed in all patients. Model of end-stage liver disease (MELD) and CP score were calculated to determine the severity of underlying liver disease [10,11]. Our study utilized baseline assessments of patients enrolled for a study designed for the development of the Clinical Covert Hepatic Encephalopathy Score (CCHE Score) for the prediction of CHE in patients with liver cirrhosis [12]. Additionally, a part of the study cohort was previously used to investigate the impact of CHE on the quality of life and sleep [8]. Therefore, specific exclusion criteria were also chosen for the present study to eliminate factors potentially influencing cognitive performance. In total, 93 patients were excluded because they fulfilled one or more of the following exclusion criteria: previous episode of overt HE (OHE) during the last six weeks, chronic alcohol consumption during the last three months, any intake of psychotropic drugs or opioids, daltonism, the presence of pre-terminal comorbidities (heart disease NYHA III-IV, chronic obstructive pulmonary disease Gold C and D, renal failure with creatinine > 1,5 mg/dl), the presence of hepatocellular carcinoma (HCC) or other active malignancies, a history of transjugular intrahepatic portosystemic shunt (TIPSS), active infection, neurological comorbidities (i.e. dementia or history of stroke), electrolyte disorders (serum potassium < 3,5 mg/dl or > 5 mg/dl, serum sodium < 130 mg/dl or > 150 mg/dl) or refusal to participate. Patients with a previous episode of OHE which took place longer than six weeks ago were allowed to participate if they were on consequent treatment with lactulose and/or rifaximin, if clinically indicated.

2.2. Diagnosis of HE

At first, every patient was examined by an experienced hepatologist to rule out OHE. The presence of HE grade 1 (HE1) was diagnosed after detailed neurological examination according to the West-Haven criteria [13]. Afterwards, portosystemic encephalopathy (PSE) syndrome test that produces the psychometric hepatic encephalopathy score (PHES) and measurement of critical flicker frequency (CFF) were performed in all patients to investigate the presence or absence of minmal HE (MHE). Interpretation of PHES was done as previously described with German norms [14]. A score < −4 was considered as pathological [14]. CFF was measured using the validated HEPAtonorm-Analyzer© 2.0 (nevoLAB GmbH, Maierhoefen, Germany). Results < 39 Hz were considered as pathological [15]. Both tests were carried out on the same day with the respective patient.

2.3. Assessment of HRQoL

To assess HRQoL we used the validated German version of the Chronic Liver Disease Questionnaire (CLDQ) [16–18]. The questionnaire contains 29 items which can be grouped into the liver-disease specific domains like activity, fatigue, worries, abdominal symptoms, emotional function and systemic symptoms. Each category can be judged separately between the groups. The results of the CLDQ score are presented on a 7-point Likert scale. Higher results indicate better quality of life.

2.4. Assessment of frailty

To assess frailty we used the clinical frailty scale (CFS), which has been evaluated recently in patients with cirrhosis [19,20]. The CFS is based on clinical judgment and divided into 9 categories (1: very fit; 2: well; 3: well with treated comorbid diseases; 4: apparently vulnerable; 5: mildly frail; 6: moderately frail; 7: severely frail; 8: very severely frail; 9: terminally ill).

2.5. Ethics

The study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The study protocol was approved by the ethics committee of the Landesärztekammer Rhineland-Palatine (Nr. 837.232.17 [11066]). Written informed consent was obtained from every participant.

2.6. Statistical analysis

Quantitative data are expressed as medians with interquartile ranges (IQR). Pairwise comparisons for quantitative variables were performed with an unpaired *t*-test or with the Mann-Whitney *U* test. Categorical variables are given as frequencies and percentages, respectively, and for the comparison of two or more patient-groups a Chi-squared test was applied.

First, the correlation of demographic and clinical variables with CLDQ total scores was assessed by means of univariable analyses. Variables with p-values < .05 in the univariable analysis were subsequently considered in a multivariable linear regression model. To reliably identify factors being associated with HRQoL, the final multivariable model was built based on a stepwise variable selection procedure.

Our complete data analysis is exploratory. Hence, no adjustments for multiple testing were performed. For all tests we used a 0.05 level to define statistically relevant deviations from the respective null hypothesis. However, due to the large number of tests, p-values should be interpreted with caution and in connection with effect estimates.

Data were analyzed using IBM SPSS Statistic Version 23.0 (Armonk, NY: IBM Corp.). All authors had access to the study data and had reviewed and approved the final manuscript.

3. Results

3.1. Demographic and clinical characteristics

A total of 218 in- and outpatients with liver cirrhosis fulfilling the inclusion and exclusion criteria were prospectively enrolled. Patients with CP A liver cirrhosis were defined as compensated (n = 133) and patients with CP B/C liver cirrhosis as decompensated (n = 85) (Table 1).

School education was higher in patients with CP A compared to patients with CP B/C liver cirrhosis (10 vs. 9 years, p = 0.030) and patients with CP B/C liver cirrhosis had a higher frequency of hepatic complications such as a history of ascites, ascites at study entry, a history of OHE, and CHE. Additionally, median sodium, albumin,

Table 1
Demographic and clinical characteristics of patients with compensated (Child-Pugh A) and decompensated (Child-Pugh B) liver cirrhosis at the time of study inclusion.

Variable		Patients with compensated (CPA) liver cirrhosis (n = 133)	Patients with decompensated (CP B/C) liver cirrhosis (n = 85)	
		n (% or IQR)	n (% or IQR)	p-value
Age in years		60 (54; 66.5)	60 (50.5; 67)	0.469
Male gender		68 (51.1)	53 (62.4)	0.104
School education		9 (9; 10)	10 (9; 12.5)	0.030
CFS		3 (2; 3)	3 (2; 4)	0.001
Active smoking		42 (31.6)	24 (28.2)	0.600
Etiology	Alcohol	31 (23.3)	38 (44.7)	0.009
	Viral hepatitis	35 (26.3)	13 (15.3)	
	NAFLD	20 (15.0)	9 (10.6)	
	Other/ mixed	47 (35.4)	25 (29.4)	
MELD score		8 (6; 10)	15 (13; 18)	< 0.001
History of ascites		40 (30.1)	69 (81.2)	< 0.001
Ascites at study entry		0 (0)	46 (54.1)	< 0.001
History of OHE		13 (9.8)	24 (28.2)	< 0.001
CHE		35 (26.3)	53 (62.4)	< 0.001
Sodium, mmol/l		139 (137; 140)	137 (135; 139)	< 0.001
Albumin, g/l		37 (34; 40)	28 (25; 32)	< 0.001
Bilirubin, mg/dl		0.9 (0.65; 1.18)	2.8 (1.4; 4.1)	< 0.001
INR		1.1 (1.0; 1.3)	1.4 (1.2; 1.7)	< 0.001
WBC, /nl		5.8 (4.4; 7.4)	5.5 (4.2; 8.1)	0.933
Hemoglobin, g/dl		13.8 (12.6; 15.1)	10.7 (9.3; 12.6)	< 0.001
Platelets, /nl		142.5 (103.3; 186.0)	102.0 (53.5; 170.5)	0.001
Ammonia, µmol/l		44.0 (35.3; 53.8) [a]	51.5 (35.3; 72.3) [b]	0.024
CRP, mg/l		2.6 (1.1; 5.0)	10 (4.5; 22.0)	< 0.001

Data are expressed as medians and interquartile ranges or as frequencies and percentages; CP, Child-Pugh; CFS, clinical frailty scale; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; CHE, covert hepatic encephalopathy; WBC, white blood cell count; CRP, c-reactive protein.
[a] Measured in 128 patients.
[b] Measured in 76 patients.

bilirubin, INR, platelets, hemoglobin, ammonia and serum levels of CRP significantly differed between both groups, whereas WBC was comparable.

3.2. Comparison of CLDQ subdomains in patients with CP A and CP B/C liver cirrhosis

Comparison of patients with compensated (CP A) and decompensated (CP B/C) liver cirrhosis revealed significant differences in CLDQ total scores (CLDQ total score: 5.6 vs. 4.8, $p < 0.001$). In addition, relevant differences were found in all subdomains-abdominal symptoms, fatigue, systemic symptoms, activity, emotional functions and worry-of the CLDQ (Table 2). Clinical meaningful differences (differences > 0.5 between two categories) were reached in the subdomains abdominal symptoms, fatigue, systemic symptoms, activity and worry.

Table 3
Uni- and multivariable analyses of predictors for quality of life in patients with compensated (Child-Pugh A) liver cirrhosis.

Variable: CLDQ total score	Univariable analysis		Multivariable analysis	
	r	p-value	B	p-value
Age	−0.023	0.790		
School education	0.110	0.209		
Female gender	**−0.231**	**0.007**	**−0.160**	**0.040**
BMI	−0.086	0.323		
CFS	**−0.196**	**0.024**	**−0.174**	**0.030**
Active smoking	**0.240**	**0.005**	**0.229**	**0.004**
History of falls during recent year	**0.298**	**< 0.001**	**0.279**	**< 0.001**
Alcoholic liver disease	0.091	0.299		
CHE	**0.218**	**0.012**	**0.179**	**0.024**
History of ascites	0.050	0.564		
MELD	−0.003	0.977		
Sodium	0.036	0.680		
Albumin	0.103	0.239		
Bilirubin	0.005	0.958		
INR	0.028	0.748		
WBC	−0.085	0.331		
Hemoglobin	0.045	0.608		
Platelets	−0.078	0.376		
Ammonia	0.044	0.621		
CRP	**−0.261**	**0.003**	**−0.161**	**0.039**

r, correlation coefficient; B, standardized beta coefficient; CP, Child-Pugh; CLDQ, chronic liver disease questionnaire; BMI, body mass index; CFS, clinical frailty scale; MELD, model for ent-stage liver disease; OHE, overt hepatic encephalopathy; CRP, c-reactive protein; CHE, covert hepatic encephalopathy; WBC, white blood cell count. Using the variables with $p < 0.05$ in the univariable analysis, the multivariable linear regression model was built with stepwise variable selection, p-values < 0.05 were considered as significant (marked in bold).

3.3. Predictors of poor HRQoL in patients with compensated (CP A) liver cirrhosis

In the univariable analysis, we could show that impaired HRQoL in patients with CP A liver cirrhosis was associated with a history of falls in the recent year, presence of CHE, female gender, active smoking, higher CFS and higher serum levels of CRP (Table 3). After inclusion of these variables into a linear multivariable regression model, all factors remained independently associated with HRQoL ($R^2 = 0.250$): history of falls in the recent year (standardized β coefficient = 0.279, $p < 0.001$), presence of CHE (standardized β coefficient = 0.179, $p = 0.024$), female gender (standardized β coefficient = −0.160, $p = 0.040$), active smoking (standardized β coefficient = 0.229, $p = 0.004$), higher CFS (standardized β coefficient = −0.174, $p = 0.030$), and higher serum levels of CRP (standardized β coefficient = −0.161, $p = 0.039$). For better visualization, CLDQ scores for patients with CP A liver cirrhosis affected by factors independently associated with HRQoL are shown in Fig. 1.

Table 2
CLDQ subdomains in patients with compensated (Child-Pugh A) and decompensated (Child-Pugh B/C) liver cirrhosis.

Variable	Patients with compensated (CP A) liver cirrhosis	Patients with decompensated (CP B/C) liver cirrhosis	p-value
CLDQ total score	5.6 (4.6; 6.1)	4.8 (3.8; 5.6)	< 0.001
Abdominal symptoms	6.3 (5.0; 7.0)	5.3 (3.7; 6.3)	< 0.001
Fatigue	4.8 (3.4; 5.8)	3.6 (2.6; 5.4)	0.002
Systemic symptoms	5.6 (4.4; 6.2)	5.0 (4.2; 5.6)	0.022
Activity	5.7 (4.7; 6.7)	5.0 (3.7; 6.0)	0.001
Emotional function	5.6 (4.6; 6.3)	5.3 (4.3; 5.9)	0.027
Worry	6.0 (5.2; 6.7)	5.2 (3.8; 6.0)	< 0.001

Data are expressed as medians and interquartile ranges; CLDQ, chronic liver disease questionnaire; CP, Child-Pugh.

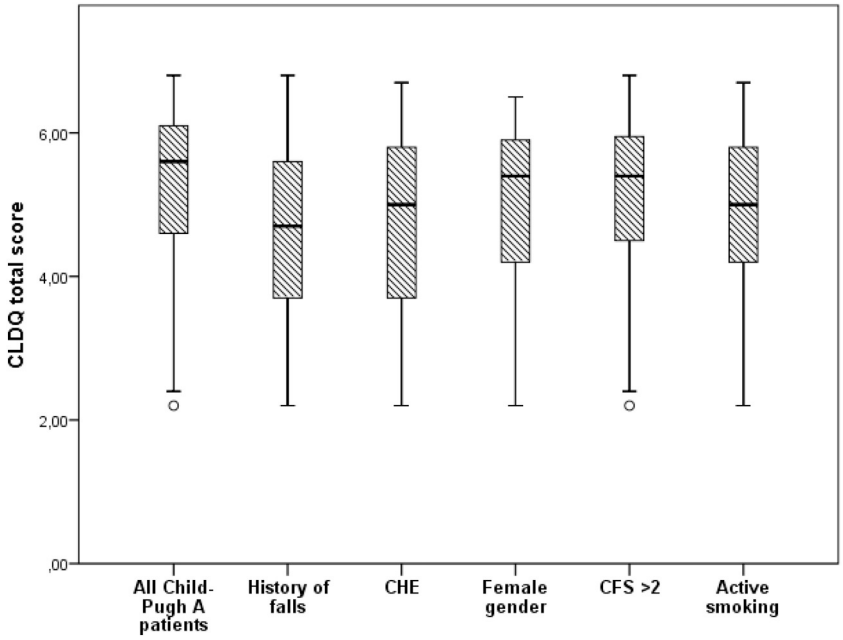

Fig. 1. Chronic liver disease questionnaire (CLDQ) total scores in patients with Child-Pugh A (CP A) liver cirrhosis, a history of falls, covert hepatic encephalopathy (CHE), female gender, clinical frailty scale (CFS) > 2 and active smoking.

3.4. Predictors of poor HRQoL in patients with decompensated (CP B/C) liver cirrhosis

In the subgroup containing patients with CP B/C liver cirrhosis, factors associated with impaired HRQoL in the univariable analysis were female gender, higher CFS, lower serum levels of potassium, a history of falls in the recent year, a history of OHE, and lower hemoglobin (Table 4). After inclusion of these variables into a linear multivariable regression model, the following factors remained independently associated with HRQoL (R^2 of 0.265): female gender (standardized β coefficient = −0.282, p = 0.005), history of OHE (standardized β coefficient = 0.235, R^2 = 0.159, p = 0.020), lower hemoglobin (standardized β coefficient = 0.316, p = 0.002). For better visualization, CLDQ scores for patients with CP B/C liver cirrhosis affected by factors independently associated with HRQoL are shown in Fig. 2.

Table 4
Uni- and multivariable analyses of predictors for quality of life in patients with decompensated (Child-Pugh B/C) liver cirrhosis.

Variable: CLDQ total score	Univariable analysis		Multivariable analysis	
	r	p-value	B	p-value
Age	−0.006	0.958		
School education	−0.175	0.109		
Female gender	**−0.303**	**0.005**	**−0.282**	**0.005**
CFS	**−0.244**	**0.026**		
Active smoking	−0.040	0.714		
History of falls during recent year	**0.286**	**0.008**		
Alcoholic liver disease	−0.059	0.595		
CHE	0.154	0.160		
History of ascites	−0.060	0.584		
Ascites at study inclusion	0.164	0.133		
History of OHE	**0.300**	**0.005**	**0.235**	**0.020**
MELD	0.121	0.271		
Sodium	**0.215**	**0.048**		
Albumin	0.154	0.160		
Bilirubin	0.205	0.060		
INR	−0.004	0.969		
WBC	0.088	0.425		
Hemoglobin	**0.424**	**< 0.001**	**0.316**	**0.002**
Platelets	−0.050	0.653		
Ammonia	0.047	0.685		
CRP	−0.195	0.075		

r, correlation coefficient; B, standardized beta coefficient; CP, Child-Pugh; CLDQ, chronic liver disease questionnaire; CFS, clinical frailty scale; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; CRP, c-reactive protein; CHE, covert hepatic encephalopathy; WBC, white blood cell count. Using the variables with p < 0.05 in the univariable analysis, the multivariable linear regression model was built with stepwise variable selection, p-values < 0.05 were considered as significant (marked in bold). BMI was not included into the analysis due to potential bias by ascites.

4. Discussion

During recent years, patient reported outcomes came more to the fore in patients with liver cirrhosis and our present prospective study confirms that HRQoL decreases with the degree of liver decompensation. In addition, we were able to show that predictors for impaired HRQoL distinctly differ between patients with compensated (CP A) and decompensated (CP B/C) liver cirrhosis. Specifically, we found potentially treatable factors that are associated with impaired HRQoL in the compensated (history of falls, presence of CHE, active smoking, higher CFS) and the decompensated (history of OHE and lower hemoglobin) stage of the disease.

Several studies documented that HRQoL is impaired in patients with liver cirrhosis when compared to the healthy general population [4,5]. Additionally, HRQoL is inversely correlated with the severity of underlying liver disease [4,6]. Our prospective study validates these findings and highlights the importance of preventive measures to delay decompensation in patients with liver cirrhosis. Obviously, this is not only important for the improvement of prognosis, but also for the improvement of HRQoL in these patients. As the management of liver cirrhosis has improved over recent years and more patients are able to survive for many years without liver transplantation despite the burden of end-stage liver disease, it is of crucial importance to identify potentially treatable factors to improve patient's reported outcomes in clinical practice.

Not surprisingly, predictive factors for impaired HRQoL distinctly differ between patients with compensated or decompensated liver

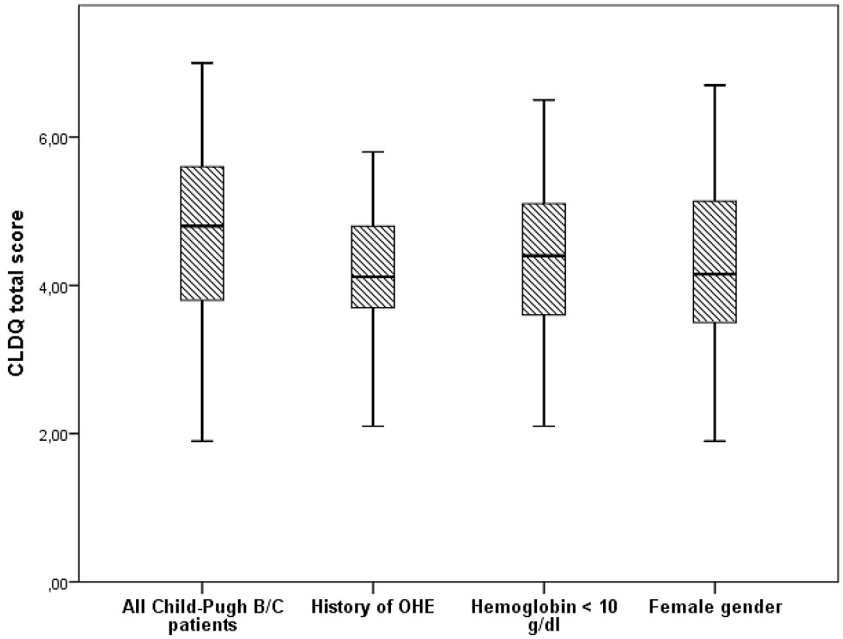

Fig. 2. Chronic liver disease questionnaire (CLDQ) total scores in patients with Child-Pugh B/C (CP B/C) liver cirrhosis, a history of overt hepatic encephalopathy (OHE), lower hemoglobin and female gender.

cirrhosis. Recent studies demonstrated that MHE or CHE are associated with impaired HRQoL [7–9]. It is an interesting finding that subclinical stages of HE (MHE, CHE) seem to affect HRQoL especially in patients with compensated liver cirrhosis. Tapper et al. found that cognitive impairment measured with the Inhibitory Control Test (ICT) was an independent predictor for impaired HRQoL in a large cohort of patients with compensated liver cirrhosis [9]. In line with our results, an Italian study showed that MHE had no impact on HRQoL in hospitalized patients with more advanced liver cirrhosis [21]. Although these studies cannot easily be compared to the present study, mainly due to differences in the included study populations and definitions of CHE, the finding that CHE particularly affects HRQoL of patients with compensated liver cirrhosis appears to be consistent throughout these studies. However, in patients with decompensated liver cirrhosis we found that a history of OHE was associated with impaired HRQoL. This finding indicates that the occurrence of an OHE episode is not only an indicator for poor prognosis but also a main driver of impaired HRQoL. Bajaj et al. showed that every OHE episode adds to a cumulative cognitive deficit that may affect daily life e.g. by causing traffic violations or the inability to work [22,23]. Since HE is often overlooked or neglected in routine clinical practice, these findings are of pivotal importance to increase alertness for this important complication of end-stage liver disease [24].

Recent studies have demonstrated that a history of falls is a major issue in patients with liver cirrhosis and is closely linked to HE [25–27]. A study by Roman et al. found that falls are generally associated with impaired HRQoL in patients with liver cirrhosis [25]. Our study emphasizes that a history of falls is a major determinant regarding an impaired HRQoL especially in patients with compensated liver cirrhosis. Although not reaching statistical significance, there is a clear trend that a history of falls is also associated with compromised HRQoL in patients with decompensated liver cirrhosis. One of the main reasons for the predictive value of a history of falls may be the psychological component associated with their occurrence. Once experienced, the history of a fall may result in constant fear of repeating falls and ultimately lead to an impaired HRQoL [28,29].

Frailty measured by the CFS is not only a valid predictor for higher mortality but also for impaired HRQoL in patients with compensated liver cirrhosis [19]. Although patients in the present study were not examined with more reliable frailty tests like the timed-up-and-go or the short physical performance battery [30,31], our findings are consistent with the study of Tapper and colleagues which examined a strict compensated population [9]. These data highlight the importance of managing frailty not only in advanced (CP B/C) but also in the early stage (CP A) of the disease. The potential relationship between impaired HRQoL and higher CFS may be complex. One determinant may be a combination of muscle weakness and other comorbidities leading to an inability to deal with tasks of daily life. It seems possible that frailty classified by the CFS is only a surrogate marker for e.g. sarcopenia which measurement was beyond the scope of the present study.

Our data revealed that female gender was associated with impaired HRQoL in compensated as well as in decompensated liver cirrhosis. This is in line with other studies investigating HRQoL in chronic liver disease [32]. One explanation may be a different self-perception of body and general health between women and men and the evident stigmatization related to the diagnosis of liver cirrhosis [7]. Here, psychological interventions may improve the perception and moreover the acceptance of the disease in women.

Furthermore, we identified an association between lower hemoglobin and impaired HRQoL in patients with decompensated liver cirrhosis. This may not be surprising since several studies identified anemia (often leading to fatigue) as a determinant for impaired HRQoL in patients with different chronic diseases like renal or cardiac failure and likewise liver cirrhosis [7,33,34]. Our data suggest that consequent treatment of anemia should play a central role in the management of patients with advanced liver cirrhosis in clinical practice.

Active smoking at study inclusion was another determinant of impaired HRQoL in patients with compensated cirrhosis. There are several data indicating that active smoking is negatively correlated with HRQoL even in an otherwise healthy population [35]. Our findings demonstrate that practitioners should become more sensitive to improve motivation to stop smoking in patients with liver cirrhosis even in the compensated stage of the disease.

Last, CRP is a widely used serum marker for the measurement of acute and chronic inflammation. Our multivariable analysis indicated an association between higher serum levels of CRP and impaired HRQoL in patients with compensated liver cirrhosis, where low-grade inflammation in the absence of infection is a common finding [36]. Our

findings are in line with data demonstrating a relationship between HRQoL and serum markers of low-grade inflammation like CRP also in studies of patients without chronic liver diseases [37]. One potential explanation why higher serum levels of CRP were not associated with impaired HRQoL in patients with decompensated liver cirrhosis may be that CRP is produced mainly by the liver and therefore is not a reliable factor in patients with more advanced stages of liver cirrhosis (CP B/C). However, mechanisms between low-grade inflammation and impairment of HRQoL cannot be judged by our data and should be investigated in future studies.

Our study has some limitations. First of all, patients included were enrolled at a single large German transplant center. Consequently, there could be a referral bias. Additionally, our findings have to be interpreted according to the study design. In this cross-sectional setting association does not mean causation. Furthermore, we excluded patients treated with opioids or benzodiazepines, which are associated with impaired HRQoL in compensated cirrhotic patients [9]. However, intake of psychotropic medication may impair results in CHE testing and lead to false positive results. Therefore, it seemed reasonable to exclude those patients also in the present study at the cost that our findings may not be generalizable to all patients with liver cirrhosis. Another point is that the cause of falls may be multifactorial. There may be a potential bias by acute alcohol intoxication, malnutrition or anemia within the previous year before study inclusion that may contribute to a higher frequency of falls in some patients. These factors could not be completely ruled out in the present study.

5. Conclusions

In conclusion, we could demonstrate in a large prospective cohort that predictors for impaired HRQoL distinctly differ between patients with compensated (CP A) and decompensated (C B/C) liver cirrhosis. Our findings indicate that a multidisciplinary intervention focusing on different factors like the management of CHE and OHE, anemia or frailty, and the prevention of falls may significantly improve patient reported outcomes in patients with all stages of liver cirrhosis. Studies aimed at treating these factors to improve quality of life in these patients should be conducted in the future.

Author contributions

Performed research: C.L., M.A.W.

Contributed to acquisition of data: C.L., Y.H., M.N., J.U.M., J.M.S., M.A.W.

Designed the experiments and analyzed the data: C.L., G.T., M.A.W.

Contributed reagents/materials/analysis tools: C.L., M.A.W., P.R.G.

Wrote the paper: C.L., M.A.W.

Statistical analysis: G.T., C.L.

All authors approved the final version of the manuscript and the authorship list.

Guarantor of the article: M.A.W.

Disclosure statement

The authors disclose no potential financial or non-financial conflict of interests

Declaration of Competing Interest

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References

[1] Schuppan D, Afdhal NH. Liver cirrhosis. Lancet 2008;371:838–51.
[2] Mokdad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med 2014;12:145.
[3] D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217–31.
[4] Marchesini G, Bianchi G, Amodio P, et al. Factors associated with poor health-related quality of life of patients with cirrhosis. Gastroenterology 2001;120:170–8.
[5] Martin LM, Sheridan MJ, Younossi ZM. The impact of liver disease on health-related quality of life: a review of the literature. Curr Gastroenterol Rep 2002;4:79–83.
[6] Sumskiene J, Sumskas L, Petrauskas D, et al. Disease-specific health-related quality of life and its determinants in liver cirrhosis patients in Lithuania. World J Gastroenterol 2006;12:7792–7.
[7] Les I, Doval E, Flavia M, et al. Quality of life in cirrhosis is related to potentially treatable factors. Eur J Gastroenterol Hepatol 2010;22:221–7.
[8] Labenz C, Baron JS, Toenges G, et al. Prospective evaluation of the impact of covert hepatic encephalopathy on quality of life and sleep in cirrhotic patients. Aliment Pharmacol Ther 2018;48:313–21.
[9] Tapper EB, Baki J, Parikh ND, et al. Frailty, psychoactive medications, and cognitive dysfunction are associated with poor patient-reported outcomes in cirrhosis. Hepatology 2018;69:1676–85.
[10] Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70.
[11] Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.
[12] Labenz C, Toenges G, Huber Y, et al. Development and validation of a prognostic score to predict covert hepatic encephalopathy in patients with cirrhosis. Am J Gastroenterol 2019;114:764–70.
[13] Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American association for the study of liver diseases and the European association for the study of the liver. Hepatology 2014;60:715–35.
[14] Weissenborn K, Ennen JC, Schomerus H, et al. Neuropsychological characterization of hepatic encephalopathy. J Hepatol 2001;34:768–73.
[15] Kircheis G, Wettstein M, Timmermann L, et al. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. Hepatology 2002;35:357–66.
[16] Schulz KH, Kroencke S, Ewers H, et al. The factorial structure of the chronic liver disease questionnaire (CLDQ). Qual Life Res 2008;17:575–84.
[17] Hauser W, Schnur M, Steder-Neukamm U, et al. Validation of the German version of the chronic liver disease questionnaire. Eur J Gastroenterol Hepatol 2004;16:599–606.
[18] Younossi ZM, Guyatt G, Kiwi M, et al. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut 1999;45:295–300.
[19] Tandon P, Tangri N, Thomas L, et al. A rapid bedside screen to predict unplanned hospitalization and death in outpatients with cirrhosis: a prospective evaluation of the clinical frailty scale. Am J Gastroenterol 2016;111:1759–67.
[20] Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–95.
[21] Moscucci F, Nardelli S, Pentassuglio I, et al. Previous overt hepatic encephalopathy rather than minimal hepatic encephalopathy impairs health-related quality of life in cirrhotic patients. Liver Int 2011;31:1505–10.
[22] Bajaj JS, Hafeezullah M, Hoffmann RG, et al. Minimal hepatic encephalopathy: a vehicle for accidents and traffic violations. Am J Gastroenterol 2007;102:1903–9.
[23] Bajaj JS, Schubert CM, Heuman DM, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. Gastroenterology 2010;138:2332–40.
[24] Labenz C, Worns MA, Schattenberg JM, et al. Epidemiology of hepatic encephalopathy in german hospitals-the EpHE study. Z Gastroenterol 2017;55:741–7.
[25] Roman E, Cordoba J, Torrens M, et al. Falls and cognitive dysfunction impair health-related quality of life in patients with cirrhosis. Eur J Gastroenterol Hepatol 2013;25:77–84.
[26] Labenz C, Toenges G, Schattenberg JM, et al. Clinical predictors for poor quality of life in patients with covert hepatic encephalopathy. J Clin Gastroenterol 2018;53:e303–7.
[27] Roman E, Cordoba J, Torrens M, et al. Minimal hepatic encephalopathy is associated with falls. Am J Gastroenterol 2011;106:476–82.
[28] Strom O, Borgstrom F, Zethraeus N, et al. Long-term cost and effect on quality of life of osteoporosis-related fractures in Sweden. Acta Orthop 2008;79:269–80.
[29] Diamond T, Stiel D, Lunzer M, et al. Osteoporosis and skeletal fractures in chronic liver disease. Gut 1990;31:82–7.
[30] Nordin E, Lindelof N, Rosendahl E, et al. Prognostic validity of the timed up-and-go test, a modified get-up-and-go test, staff's global judgement and fall history in evaluating fall risk in residential care facilities. Age Ageing 2008;37:442–8.
[31] Volpato S, Cavalieri M, Sioulis F, et al. Predictive value of the short physical performance battery following hospitalization in older patients. J Gerontol A Biol Sci Med Sci 2011;66:89–96.
[32] Huber Y, Boyle M, Hallsworth K, et al. Health-related quality of life in non-alcoholic fatty liver disease associates with hepatic inflammation. Clin Gastroenterol Hepatol 2018;17:2085–92.
[33] Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000;35:1737–44.
[34] Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071–84.
[35] Goldenberg M, Danovitch I, IsHak WW. Quality of life and smoking. Am J Addict 2014;23:540–62.
[36] Tilg H, Cani PD, Mayer EA. Gut microbiome and liver diseases. Gut 2016;65:2035–44.
[37] Garvin P, Nilsson E, Ernerudh J, et al. The joint subclinical elevation of CRP and IL-6 is associated with lower health-related quality of life in comparison with no elevation or elevation of only one of the biomarkers. Qual Life Res 2016;25:213–21.