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Health-related quality of life in NAFLD is determined by lobular inflammation on liver biopsy: data from the European NAFLD Registry

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Abstract

Introduction: Chronic liver disease exerts a negative impact on health-related quality of life (HRQL). The role of clinical and histological disease activity on HRQL remains undetermined. The aim of this study was to explore the influence of liver histology in NAFLD on HRQL.

Methods: Patients with histological defined NAFLD were enrolled prospectively into the European NAFLD Registry at three centres in Germany, the UK and Spain. The chronic liver disease questionnaire (CLDQ) was completed within 6 months of diagnostic liver biopsy.

Results: 304 patients with a mean age of 52.3 (±12.9) years were included. Mean CLDQ overall score was 5.0±1.2 with the lowest score in the category fatigue (4.3±1.6) and the highest scores for activity (5.4±1.4). Women exhibited significantly lower CLDQ compared to men (4.6±1.3 vs. 5.3±1.1, $p<0.001$). Reflecting lower HRQL, there was a negative correlation between CLDQ score and presence of obesity ($p<0.001$), type 2 diabetes ($p<0.001$) and dyslipidaemia ($p<0.01$). AST but not ALT was negatively correlated with HRQL. Histological features of NAFLD had a significant impact on HRQL: increasing histological scores of steatosis (1 vs. 3: 5.3±1.1 vs. 4.5±1.4, $p<0.01$) and lobular inflammation (0 vs. 3: 5.3±1.2 vs. 3.9±1.8, $p<0.001$) were associated with lower HRQL. In contrast, this was not observed in patients with advanced fibrosis in comparison to early or intermediate fibrosis (F3-4 vs. F0-2: 4.9±1.2 vs. 5.1±1.3, $p=0.072$). By multivariate analysis, gender, age, type 2 diabetes and lobular inflammation were independently associated with low HRQL.

Discussion: There is a substantial symptom burden in patients with NAFLD. In addition to age, gender and the presence of diabetes, lobular inflammation on liver biopsy is correlated with poorer HRQL, even in the absence of cirrhosis. With emergent pharmacological treatment options for NASH, HRQL will be of great relevance to determine a patient's benefit from treatment.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- NAFLD is the most prominent liver disease, but the disease burden is not well defined.
- Inflammation can affect general well-being and the quality of life.

WHAT IS NEW HERE

- Lobular inflammation on liver biopsy is an independent predictor of impaired health-related quality of life (HRQL) in NAFLD.
- Females with NAFLD report a significantly higher impairment of HRQL compared to men.
- Obesity and diabetes type 2 are the comorbidities that impair HRQL in NAFLD.
- In Europe country-specific differences in the disease activity and HRQL exist.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the fastest growing and most common cause of liver disease globally (1). In Europe it is estimated to affect up to 30% of the population (2) and a continued increase has been predicted in the coming years (3). NAFLD constitutes a disease spectrum that has been defined histologically by characteristic lesions, including accumulation of fat in more than 5% of hepatocytes, the presence of lobular inflammation and hepatocyte injury characterizing the grade of non-alcoholic steatohepatitis (NASH) and varying degrees of fibrosis (4). The stage of the disease is defined by histological criteria and previous studies have focused on the role of these histological findings to predict the prognosis. Among these, the stage of fibrosis as defined by the currently used 5-tier (0-4) histological staging, which is in cooperated in the two commonly used histological scoring systems, the NASH CRN activity score (NAS) (5) and the Steatosis-Activity-Fibrosis (SAF) score (6), correlates with hepatic morbidity and overall survival (7). Today, NASH is the most rapidly growing and the second leading indication for liver transplantation in the US (8). Overall mortality in patients with NASH is strongly influenced by comorbidities, including abdominal obesity, arterial hypertension, insulin resistance and dyslipidaemia (9).

Patients suffering from chronic liver disease exhibit unspecific symptoms, but commonly report fatigue and abdominal discomfort. These symptoms can add to the disease burden and lead to a significant impairment in the quality of life (10). In chronic hepatitis C, it has been proposed that these effects add to the economic burden of the disease by increasing leave time from work and loss in productivity (11). Previous studies in patients with NAFLD observed an association between fatigue and day time sleepiness with the degree of insulin resistance but not with the histological disease severity (12). In an US population, NAFLD and NASH caused an incremental decrease of physical health scores using the SF-36 survey. In this analysis, no association of NASH or mental health scores with the degree of fibrosis were reported (13). With the emergence of medical therapy for NASH, a cost-benefit debate can be expected, and it will be of importance to identify patients with the highest unmet need for treatment. Patient-reported outcomes (PRO) are an important tool to assess the individual burden of a disease. Different tools have been developed to assess health-related quality of life (HRQL). The chronic liver disease questionnaire (CLDQ) is a liver disease-specific,

multidimensional concept, which evaluates emotional, mental, physical and social functioning categories (14, 15). It therefore more specifically addresses symptoms of patients with chronic liver disease – including extrahepatic manifestations – compared to traditional HRQL measures, such as the SF-36 health survey questionnaire (15-17). Lower CLDQ scores indicate worse self-reported quality of life. Using the CLDQ, a decreased HRQL was observed in a cohort study on 150 patients with non-infectious chronic liver disease which frequently reported symptoms including fatigue, abdominal discomfort and anxiety (18). In patients with HCV an improvement of HRQL following sustained virological response (SVR) from directly acting antivirals (DAA) was detectable using the CLDQ (19). Viremia and hepatic inflammation are likewise associated with impaired HRQL in patients with chronic HBV (20). Beyond disease-specific aspects, HRQL can be influenced by national and social factors, but a good generalizability has recently been shown for other tests, suggesting that PROs can be reliably assessed and compared even between different countries (21). The aim of this prospective study was to determine factors that affect HRQL in European patients with histological defined NAFLD.

Material and Methods

Patient characteristics

Patients with NAFLD were recruited at the University Medical Centre of the Johannes Gutenberg-University Mainz (UMCM), Germany, at the Freeman Hospital Liver Unit, Newcastle Upon Tyne Hospitals NHS Trust, Newcastle upon Tyne (UNEW), United Kingdom, and at the University Hospital of the University of Seville, Spain, as part of the prospectively enrolling European NAFLD Registry, after written informed consent was obtained. Permission was obtained from the respective ethical commissions: Ethikkommission der Landesärztekammer Rheinland-Pfalz (Germany), the North East–Tyne & Wear South Research Ethics Committee (UK) and the Spanish authorities. Other causes of liver disease were ruled out by serological testing, and no patients exhibited decompensated liver cirrhosis. Thresholds for alcoholic consumption were defined according to the EASL guidelines (22). The prevalence of type 2 diabetes, arterial hypertension, hyperlipidaemia and the presence of the metabolic syndrome were defined according to the Joint

Scientific Statement for Harmonizing the Metabolic Syndrome (23). Obesity was defined as BMI ≥ 30 kg/m^2. Laboratory results were obtained at the time of attendance and were considered missing if not available within a maximum of 30 days of the liver biopsy.

Histological analysis

All liver histology was assessed by central scoring from expert histopathologists who have meet in person and synchronized scoring (BS und DT). NASH was diagnosed and subsequently scored according to the NASH CRN criteria (5). Histological scoring included hepatic steatosis graded into 3 grades: grade 1: 5-33% of hepatocytes affected, grade 2: 33%-66% of hepatocytes affected, and grade 3: >66% of hepatocytes affected. Lobular inflammation grade 0: no inflammatory foci, grade 1: < 2 foci per 200×field, grade 2: 2-4 foci per 200×field, and grade 3: > 4 foci per 200×field; ballooning grade 0: no ballooned hepatocytes, grade 1: a few ballooned hepatocytes, and grade 2: many/prominent ballooned hepatocytes; and fibrosis stage (F) 0: no fibrosis, F1: perisinusoidal, perivenular, or portal/periportal fibrosis, F2: perisinusoidal and portal/periportal fibrosis, F3: bridging fibrosis, and F4: cirrhosis. The NAFLD activity score (NAS) was calculated as the sum of the scores for steatosis (1-3), lobular inflammation (0-3), and ballooning (0-2), ranging from 1 to 8 (5).

Chronic Liver Disease Questionnaire

For health-related quality of life (HRQL) the liver disease-specific questionnaire "Chronic Liver Disease Questionnaire (CLDQ)" was used in the respective language (14, 15). The CLDQ consists of 29 items on a seven-point Likert scale ranging from 1 (all of the time) to 7 (none of the time) representing the frequency of clinical symptoms and emotional problems associated with chronic liver diseases in the last two weeks. It is divided into six subscale scores (abdominal symptoms, fatigue, systemic symptoms, activity, emotional functioning, worry) and a CLDQ overall score. By dividing each domain score by the number of items in the domain, CLDQ results can be presented on a 1–7 scale with 1 indicating worst HRQL (bad) and 7 indicating best HRQL (good). Patients completed the questionnaire during regular outpatient visit and within 6 months of the diagnostic liver biopsy.

Statistical analysis

Descriptive statistics were computed for all variables. These include means and standard deviations or medians and 25th and 75th percentiles for continuous factors. For categorical variables, frequencies and percentages were calculated. Spearman's rank correlation coefficient was calculated to compare lab values and CLDQ scores. Univariate regression analysis was used to examine association between two variables. Differences between two groups were calculated by Mann-Whitney-U-rank test or the Fisher's Exact test. $\chi 2$ test, resp. Kruskal-Wallis rank test was used for multi-group comparison. Analysis of covariance (ANCOVA) was performed for multivariate testing accounting for the confounders country, gender, age, BMI, and type 2 diabetes. All tests were two-tailed, with a significant p value defined as <0.05. Univariate analyses were performed by using IBM SPSS Statistic Version 21.0 (Armonk, NY: IBM Corp.). The ANCOVA was performed by means of SAS, Version 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics

A total of 304 patients were included in the study, 154 from the UK, 133 from Germany and 17 from Spain. The mean age was 52.3 (± 12.9) years and 53.3% (n=162) were male. The majority of patients (n=228, 75.0%) were obese with a median BMI of 33.3 kg/m² (IQR: 30.0; 37.5). Demographic data, characteristics of liver function, histopathological features and differences between the countries are presented in **Table 1**. The majority of patients had moderate steatosis (steatosis grade 2, n=152 (51.4%)), none or low-grade lobular inflammation (grade 0 or 1, n=162 (54.7 %)) and none or low-grade fibrosis stage (stage 0 to 2, n=177, (58.2%)) on liver biopsy.

Differences in health-related quality of life in Europe

A comparison between the three enrolling European countries showed significant differences between the populations (summarized in **Table 1)**. Patients in the UK (median (range) 56y (17-77)) and Spain (median (range) 61y (33-74)) were older compared to the entire population. Likewise, rates of obesity (total cohort vs UK: 75% vs. 86%; p<0.001) and type 2 diabetes (total cohort vs UK: 51.3% vs 61.7%; p<0.01) were higher, while arterial hypertension (total cohort vs UK: 56.5% vs. 66.8%;

p<0.001) was lower in the UK cohort. Interestingly there were also significant differences in health-related quality of life between the three European countries. In the UK, the lowest CLDQ overall score was observed in comparison to the overall cohort (mean (SD) 4.73 (±1.3) vs. 4.99 (±1.2); p<0.01).

Table 1. **Demographic data, characteristics of liver function, histological features and differences between the sub-cohorts**

Parameter	Total (n=304)	UK cohort (n=154)	German cohort (n=133)	Spanish cohort (n=17)	P
Male gender*	162 (53.3)	87 (56.5)	69 (51.9)	6 (35.3)	0.82
Age (range)	54 (17-77)	56 (17-77)	53 (21-75)	61 (33-74)	**<0.05**
BMI#	33.3 (30.0; 37.5)	35 (31.6; 38.7)	31.9 (28.7; 36.3)	31.2 (27.3; 37.0)	**<0.001**
Obesity*	228 (75.0)	133 (86.4)	85 (63.9)	10 (58.8)	**<0.001**
Diabetes type 2*	156 (51.3)	95 (61.7)	52 (39.1)	9 (52.9)	**<0.01**
Hypertension*	203 (66.8)	87 (56.5)	102 (76.7)	14 (82.4)	**<0.001**
Hyperlipidemia*	177 (58.2)	88 (57.1)	83 (62.4)	6 (35.3)	0.07
ALT#	73 (48; 110)	73 (48; 109)	81 (51; 110)	33 (24; 61)	**<0.01**
AST#	50 (36; 69)	50 (38; 71)	51 (37; 68)	29 (24; 54)	**<0.01**
γ-GT#	84 (56; 162)	92 (59; 164)	80 (53; 161)	82 (45; 223)	0.5
Albumin#	43 (40; 45)	44 (43; 47)	41 (39; 43)	45 (43; 47)	**<0.001**
Platelet count#	233 (183; 283)	240 (190; 296)	226 (183; 270)	190 (176; 228)	0.05
Ferritin#	154 (79; 313)	130 (68; 255)	220 (117; 357)	97 (51; 155)	**<0.001**
HbA1c#	6.1 (5.5; 7.1)	6.3 (5.75; 7.6)	5.7 (5.3; 6.3)	6.5 (6.2; 7.4)	**<0.001**
Histological findings					
NASH	210 (69.1)	109 (70.8)	89 (66.9)	12 (70.6)	0.77
Steatosis 1/2/3	100/152/44	34/79/34	58/67/7	8/6/3	**<0.001**
Ballooning 0/1/2	82/163/51	44/72/31	34/81/17	4/10/3	0.26
Lobular inflammation 0/1/2/3	63/162/68/3	27/68/49/2	32/87/12/1	4/7/6/0	**<0.001**
Fibrosis 0/1/2/3/4	36/74/67/82/45	29/29/28/40/28	5/43/36/37/12	2/2/3/5/5	**<0.001**

Data are expressed as *number (percentage) or #median (25th, 75th percentiles). Histological findings were scored according to the criteria proposed by Kleiner et al (5). Comparisons between cohorts were carried out using the $\chi 2$- or Kruskall-Wallis test.
ALT (normal range -<50 U/l), AST (normal range 5-35 U/l), γ-GT (normal range 12-64 U/l), Albumin (normal range 34-48 g/l), platelet count (normal range 150-450/nL); Ferritin (normal range 20-275ng/ml), HbA1c (normal range 4.1-5.6%), Obesity is defined as BMI >30kg/m^2.

Health-related quality of life and influencing factors

Mean CLDQ overall score was 4.99 (±1.2) in the entire study population. The lowest scores were reported in the subcategory "fatigue" with a value of 4.31 (±1.6), followed by "emotional functioning" with 4.93 (±1.5). "Abdominal symptoms" and "activity" showed the highest values with 5.33 (±1.6) and 5.43 (±1.4) **(Table 2)**. Women exhibited a significantly lower CLDQ overall score than men (mean (SD) 4.62 (±1.3) vs. 5.31 (±1.1); p<0.001). Also, all CLDQ subscale scores including abdominal symptoms, fatigue, systemic symptoms, activity, emotional functioning, and worry were significantly lower in women compared to men (p<0.01) **(Table 2)**. No correlation existed between CLDQ overall score and age **(Table 3)**. Reflecting lower HRQL, there was a negative correlation between overall CLDQ score and obesity (p<0.001), type 2 diabetes (p<0.001) and dyslipidaemia (p<0.01) **(Table 3)**. AST (r = -0,12, p<0.05) correlated significantly with CLDQ, while there was no correlation regarding ALT (r = 0.04) or gGT (r = -0.08). Interestingly, there was a positive correlation with the acute phase response protein Ferritin and CLDQ overall score (r = 0.166; p<0.01), while HbA1c exhibited a negative correlation with lower HRQL (r=-0.26; p<0.001) **(Table 3)**.

With regards to the subscale scores, fatigue scored the lowest compared to all other sub-categories in all three countries **(Suppl. Table 1)**.

Table 2. **Differences in health-related quality of life concerning gender aspects**

Parameter	**Total (n=304)**	**Male (n=162)**	**Female (n=142)**	**p**
CLDQ overall score	4.99 (±1.2)	5.31 (±1.1)	4.62 (±1.3)	**<0.001**
Abdominal symptoms	5.33 (±1.6)	5.69 (±1.4)	4.92 (±1.7)	**<0.001**
Fatigue	4.31 (±1.6)	4.61 (±1.5)	3.96 (±1.5)	**<0.001**
Systemic symptoms	5.09 (±1.3)	5.43 (±1.2)	4.71 (±1.3)	**<0.001**
Activity	5.43 (±1.4)	5.79 (±1.3)	5.02 (±1.4)	**<0.001**
Emotional functioning	4.93 (±1.5)	5.27 (±1.4)	4.54 (±1.5)	**<0.001**
Worry	5.18 (±1.5)	5.45 (±1.3)	4.86 (±1.6)	**<0.01**

Data are expressed as means and standard deviations. Comparisons between groups were carried out using the Mann-Whitney U test.

Table 3. CLDQ in relation to the presence or absence of patient characteristics and laboratory results

Characteristics	CLDQ overall score: Characteristic present	CLDQ overall score: Characteristic absent	p-value
Age ≥54years	4.94 (±1.2)	5.05 (±1.3)	0.37
Obesity (BMI>30)	4.83 (±1.2)	5.46 (±1.1)	**<0.001**
Diabetes type 2	4.74 (±1.2)	5.25 (±1.2)	**<0.001**
Hypertension	4.97 (±1.2)	5.04 (±1.3)	0.51
Hyperlipidemia	4.84 (±1.2)	5.24 (±1.2)	**<0.01**

	Correlation coefficient (r) with CLDQ score	p-value
ALT	0.04	0.53
AST	-0.12	**0.04**
γ-GT	-0.08	0.16
Albumin	<0.01	0.97
Platelet count	-0.12	0.05
Ferritin	0.17	**<0.01**
HbA1c	-0.26	**<0.001**

Data presented in means and standard deviations; Obesity is defined as BMI >30kg/m^2; ALT = alanine aminotransferase; AST = aspartate aminotransferase, γ-GT = γ-glutamyltransferase.
Statistical dependence between parameters of the metabolic syndrome and CLDQ was measured by Mann-Whitney-U-rank test; to compare laboratory levels and CLDQ score Spearman's rank correlation coefficient was performed.

Impact of histological features of NAFLD on health-related quality of life

NASH was present in 210 patients (69.1%). The distribution of NASH in male and female was equal. Obesity (54.9% vs. 20.1%; p<0.05) and type 2 diabetes (39.9% vs. 11.5%; p<0.01) were more prevalent in NASH in comparison to NAFL. There were no significant differences with regard to age, hypertension, dyslipidaemia or hyperferritinemia. With regards to standard labs, AST (p<0.001), ALT (p<0.05) and HbA1c (p<0.001) were significantly higher in NASH compared to NAFL. NASH was associated with a significant lower HRQL compared to patients with NAFL (mean (SD): 4.85 (±1.3) vs. 5.31 (±1.1); p<0.01). Additionally, patients with NASH scored significantly lower on all CLDQ subscales, except for "abdominal symptoms" and "emotional function" (**Table 4**).

The histological features of NAFLD on liver biopsy had a significant impact on HRQL. Patients with more severe hepatic steatosis exhibited a lower HRQL score (grade 3 vs. grade 1: 4.5 (±1.4) vs. 5.3 (±1.1); $p<0.05$). Similarly, more severe ballooning (grade 2 vs. grade 0: 4.7 (±1.3) vs. 5.3 (±1.2); $p<0.05$) and severe lobular inflammation (grade 3 vs. grade 0: 3.9 (±1.8) vs. 5.3 (±1.2); $p<0.001$) were associated with lower HRQL. Advanced fibrosis and compensated cirrhosis (F3/F4) were observed in 127 patients (41.8%). In these patients, a trend towards lower HRQL compared to patients with early or intermediate fibrosis (F0-2) (F3-4 vs. F0-2: 4.9 (±1.2) vs. 5.1 (±1.3); $p=0.07$) was observed. However, in contrast to features of steatohepatitis, this did not reach statistical significance. **Figure 1** summarizes the histological features and the associated CLDQ overall scores.

Table 4. **Comparison of health-related quality of life in NAFL and NASH**

Parameter	Total (n=304)	NAFL (n=94)	NASH (n=210)	p
CLDQ overall score	4.99 (±1.2)	5.31 (±1.1)	4.85 (±1.3)	**<0.01**
Abdominal symptoms	5.33 (±1.6)	5.64 (±1.3)	5.19 (±1.7)	0,088
Fatigue	4.31 (±1.6)	4.76 (±1.5)	4.10 (±1.6)	**<0.01**
Systemic symptoms	5.09 (±1.3)	5.45 (±1.2)	4.93 (±1.4)	**<0.01**
Activity	5.43 (±1.4)	5.74 (±1.3)	5.29 (±1.4)	**<0.01**
Emotional functioning	4.93 (±1.5)	5.15 (±1.5)	4.83 (±1.5)	0,067
Worry	5.18 (±1.5)	5.47 (±1.5)	5.04 (±1.5)	**<0.05**

Data are expressed as means and standard deviations. Comparisons between groups were carried out using the Mann-Whitney U test.

On multivariate analysis, after correction for confounders including country, gender, age, BMI, and type 2 diabetes, an independent association between impaired HRQL and hepatic inflammation ($p<0.05$) but not fibrosis ($p=0.47$) was detected. Also, gender ($p<0.0001$), age ($p<0.05$), BMI ($p<0.001$) and type 2 diabetes ($p<0.01$) were independently associated with impaired HRQL.

Discussion

The current study explored HRQL in patients with biopsy proven NAFLD from three European centers. HRQL is an important facet when assessing the burden of a chronic disease. Despite the lack of specific symptoms in liver disease, patients can experience severe impairment in the quality of life at an individual level (24). In patients with NAFLD and other chronic liver disease, fatigue and impaired sleeping quality are the most frequently reported finding (12, 24, 25). Likewise, the number of comorbidities and medications are negatively correlated with HRQL in patients with chronic liver disease (18). The striking finding of the current analysis in this well characterized European cohort was that - in contrast to the published data on predictors of overall and liver specific mortality - lobular inflammation correlated independently with HRQL (7, 26). This was previously not reported in the NASH-CRN cohort published in 2009, which found lower HRQL using the generic short form-36 (SF-36) in NASH compared to a healthy US population and a significant effect in cirrhosis only (13). The apparent divergence of fibrosis on mortality and HRQL is intriguing and potentially reflects differences in the underlying pathogenic mechanisms that contribute to progression of the respective histological lesion and the loss in quality of life in NAFLD. Metabolic inflammation creates a milieu in which liver cell injury and fibrogenesis occur and drive disease progression over years. Various studies have identified hepatic fibrosis, but not inflammation or steatosis on liver biopsy as the histological feature that correlates best with overall and liver-related mortality (7, 26). Although inflammation and steatosis are prerequisites for the diagnosis and disease progression, these features are more dynamic compared to hepatic fibrosis. Hepatic fibrosis on the other hand reflects an aggregate of liver injury that builds up over time and can be detected on liver biopsy despite sampling variability. Nonetheless, the disease activity in NASH – namely inflammation and ballooning – has been linked to elevated cytokine levels and markers of systemic inflammation (27). These inflammatory marker and metabolic stress are known to negatively affect the mood and promote depressive symptoms (28, 29).

Data from clinical trials in chronic HCV or HBV infection support a dominant role of inflammation on HRQL. Viral elimination respectively suppression following antiviral therapy was

associated with improved HRQL, arguing for an effect of inflammation on patient reported outcomes, while improvement of fibrosis did not affect HRQL (20, 30, 31). Also, improvement of HRQL was comparable in patients with early and advanced fibrosis following cure using DAAs (31). In a recent trial in patients with histologically confirmed NASH and fibrosis stage 2 or 3 an improvement of fibrosis by at least one stage, resulted in an improvement in HRQL measures (32). Beyond histological findings, a significant negative impact of metabolic comorbidities, including the presence of type 2 diabetes or dyslipidemia, on HRQL was observed. In line with the published data, *fatigue* was the most frequently reported symptom (12, 24, 33).

The burden of disease for NAFLD is high and an exponential increase in Europe is predicted in the next years (34). In Germany, France, Italy and United Kingdom there are approximately 52 million people living with NAFLD and the connected annual cost have been estimated around 35 billion Euro. These costs arise from liver-related morbidity and associated comorbidities that amount to spending in health-care but also indirect cost related to work productivity (35). Currently, clinical trials in phase II and III are being conducted and assess the resolution of steatohepatitis and improvement or stabilisation of hepatic fibrosis as a primary endpoint (36). Based on the current analysis it can be expected, that improvement of steatohepatitis – and in particular lobular inflammation – will have measurable effects on HRQL even independently of fibrosis improvement.

The current study observed a strong influence of gender on HRQL. Women scored lower in all subcategories of the CLDQ across three European countries, indicating that the burden of disease in women could be higher. This effect was not explained by disease activity, as the frequency of early and advanced stages and disease activity were comparably between gender. Interestingly, these findings are replicated in studies on HCV and HIV co-infected patients that also showed significantly lower HRQL in women (19). Thus, it seems plausible that CLDQ has a higher sensitivity to detect impairment in the quality of life in women compared to men. Future tools of HRQL will have to account for this gender-specific difference.

The CLDQ not only assesses symptoms but also social and emotional factors at a superficial level using 4-5 questions in the respective sub-sections. Therefore, it has proven particularly feasible

in an outpatient setting with limited time resources. The CLDQ represents a disease-specific tool with the capability to detect subtle disease-specific aspects that are missed by more commonly used generic tools. On the other hand, a comparison with the general population is not possible (37). Nonetheless, the ability of the CLDQ to differentiate more subtle can be questioned as most patients scored within a range of 2.5 points on this 7-point Likert scale. The development of a novel disease-specific tool specifically to assess HRQL in NASH will be required to assess subtler changes, especially in RCTs. These novel tools should focus on the major symptom burden in NASH, which is related to loss of energy and fatigue, comorbidities, including diabetes and obesity, and also adjust for the strong gender differences. Beyond the assessment of treatment response, HRQL can be useful in prioritizing patients for lifestyle interventions or pharmacological therapies in the future.

In summary, the current study highlights the link of impaired HRQL with liver parenchymal inflammation in patients with NAFLD from northern, middle and southern Europe. These findings contradict frequent perception, that patients suffering from chronic liver disease are asymptomatic. Our findings underline the need for an appropriate tool to assess the symptoms that contribute to the high disease burden in NASH. As NAFLD is a highly prevalent disease that causes a distinct loss in HRQL and eventually also poses an economic burden, a high priority should be placed on prevention and treatment. With the emergence of medical therapy, the improvement in HRQL will likely influence the choice of drug in the future.

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Figures and tables

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Table 3: CLDQ in relation to patient characteristics and laboratory results

Table 4: Comparison of health-related quality of life in NAFLD and NASH

Figure 1: Impact of histological features of NAFLD on health-related quality of life, (A) steatosis grading, (B) ballooning grading, (C) lobular inflammation grading, (D) fibrosis grading

Supplementary Table 1: Comparison of health-related quality of life in Germany, UK and Spain.

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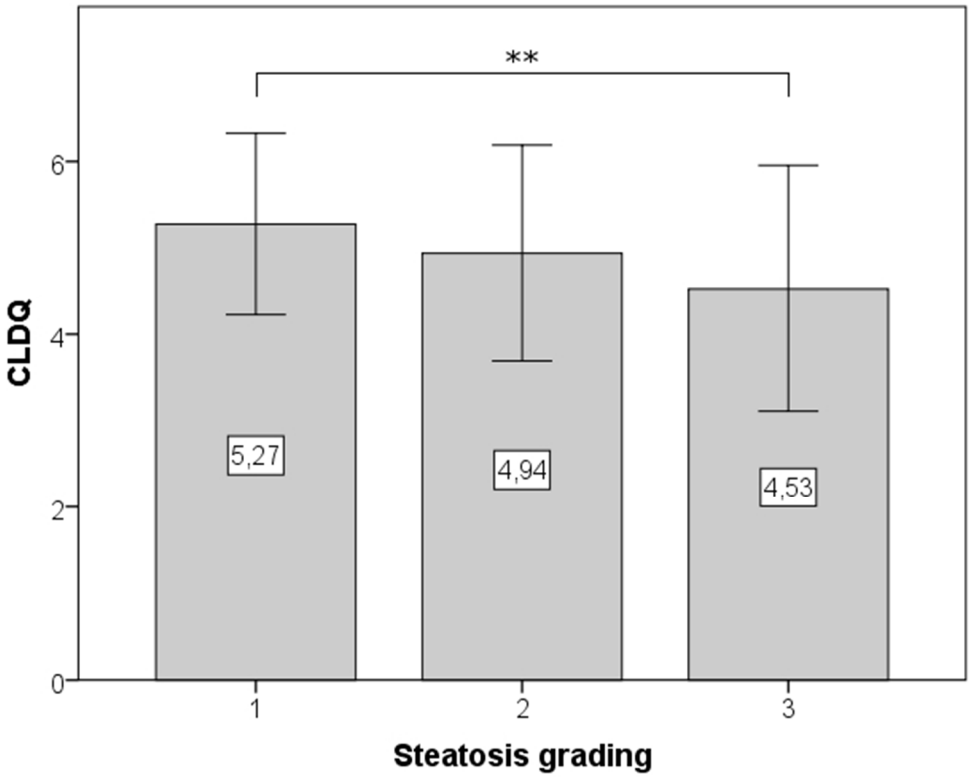

Impact of histological features of NAFLD on health-related quality of life, (A) steatosis grading, (B) ballooning grading, (C) lobular inflammation grading, (D) fibrosis grading

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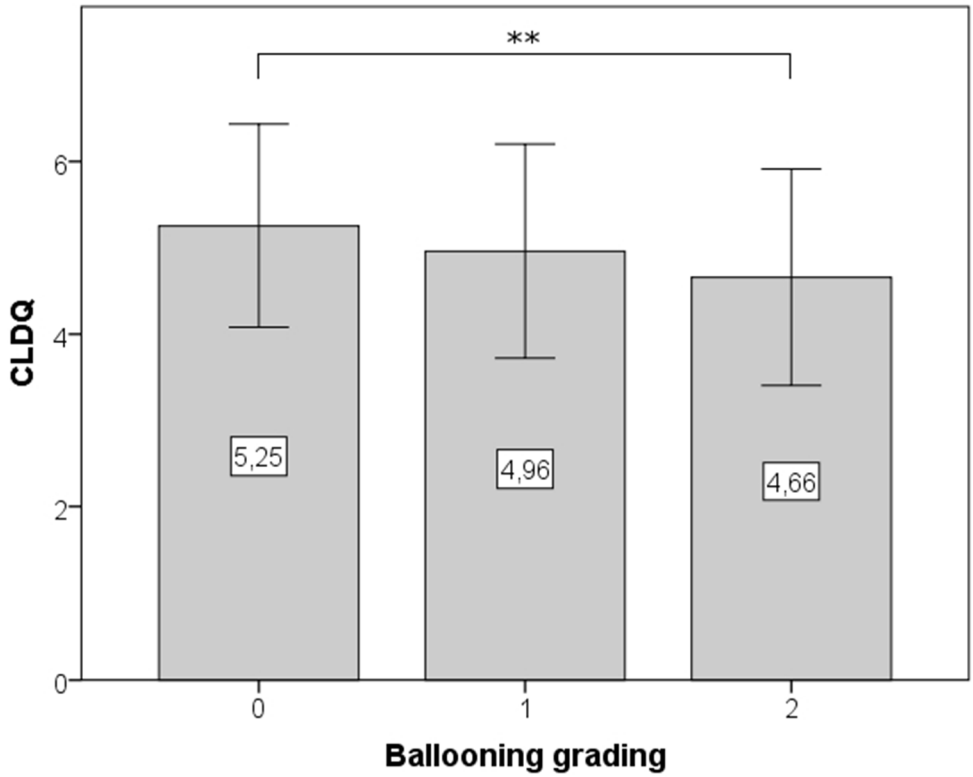

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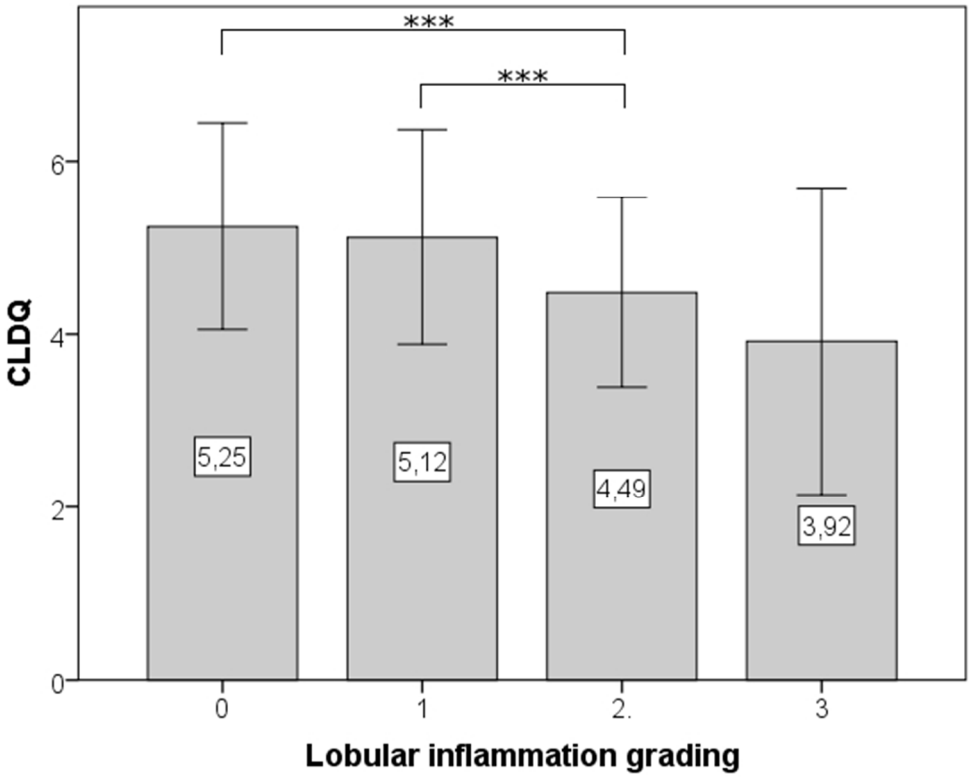

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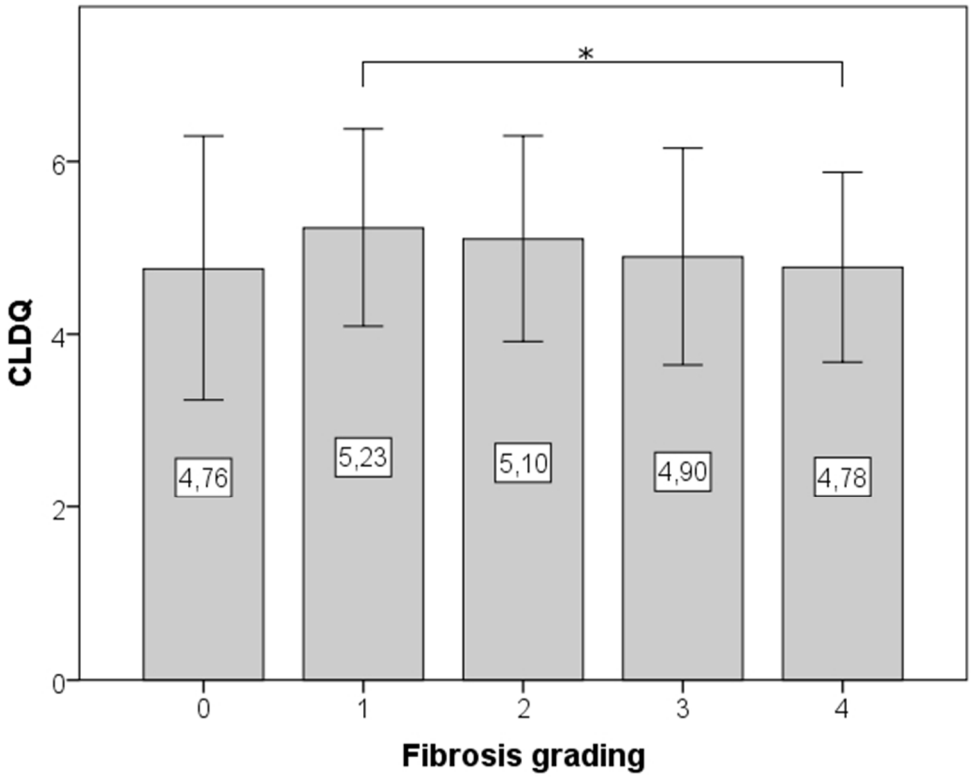

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221x177mm (72 x 72 DPI)

Supplementary Table 1. **Comparison of Health-related quality of life in sub-cohorts**

Parameter	Total (n=304)	UK cohort (n=154)	German cohort (n=133)	Spanish cohort (n=17)	p
CLDQ overall score	4.99 (±1.2)	4.73 (±1.3)	5.27 (±1.1)	5.14 (±1.1)	**<0.01**
Abdominal symptoms	5.33 (±1.6)	5.24 (±1.6)	5.51 (±1.5)	4.76 (±1.6)	0.12
Fatigue	4.31 (±1.6)	4.12 (±1.6)	4.48 (±1.5)	4.64 (±1.7)	0.09
Systemic symptoms	5.09 (±1.3)	4.82 (±1.4)	5.37 (±1.2)	5.35 (±1.2)	**<0.01**
Activity	5.43 (±1.4)	5.21 (±1.5)	5.73 (±1.2)	5.12 (±1.4)	**<0.01**
Emotional functioning	4.93 (±1.5)	4.57 (±1.6)	5.30 (±1.3)	5.32 (±1.4)	**<0.001**
Worry	5.18 (±1.5)	4.91 (±1.7)	5.46 (±1.3)	5.38 (±1.1)	**<0.01**

Data are expressed as means and standard deviations. Comparisons between cohorts were carried out using the Kruskal-Wallis test.