Health-related Quality of Life in Patients With Nonalcoholic Fatty Liver Disease: A Prospective Multi-center UK Study

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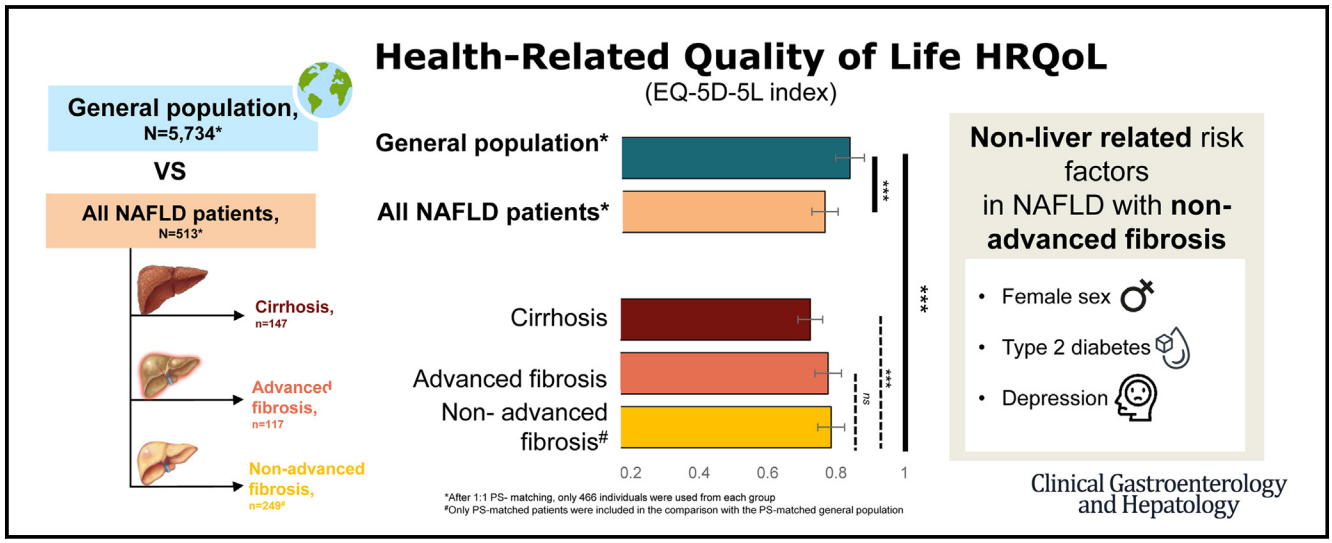

BACKGROUND & AIMS: It is unclear whether health-related quality of life (HRQoL) is impaired in patients with nonalcoholic fatty liver disease (NAFLD) without advanced fibrosis and how this compares with the general population. We aimed to assess HRQoL in patients with NAFLD in comparison to the general population and any associations of fibrosis severity and metabolic comorbidities with impairments in HRQoL.

METHODS: We prospectively enrolled 513 consecutive patients with NAFLD who completed the EuroQol 5-dimensional questionnaire (EQ-5D) and Chronic Liver Disease Questionnaires (CLDQ). Demographic and clinical information, liver biopsy results, and/or liver stiffness (LS) by transient elastography were recorded. A general population sub-cohort of the Health Survey for England 2018 was used as a comparator (n = 5483), and a 1:1 propensity-score (PS) matching was performed, according to age, sex, body mass index, and type 2 diabetes mellitus (T2DM).

RESULTS: EQ-5D-5L utility was significantly lower in 466 PS-matched patients with NAFLD compared with PS-matched controls (0.77 ± 0.27 vs 0.84 ± 0.19; $P < .001$), even in those without advanced

Abbreviations used in this paper: BMI, body mass index; CLDQ, Chronic Liver Disease Questionnaire; EQ-5D, EuroQol 5-dimensional questionnaire; F, fibrosis stage; HRQoL, health-related quality of life; HSE, Health Survey for England; LS, liver stiffness; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PS, propensity score; SF-36, Short Form 36; T2DM, type 2 diabetes mellitus; UK, United Kingdom; VAS, visual analog scale.

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fibrosis (F ≤2 or LS <8kPa) (0.80 ± 0.24 vs 0.84 ± 0.19; $P = .024$). HRQoL measures (EQ-5D-5L, EQ-VAS, CLDQ) did not differ between patients with NAFLD with and without advanced fibrosis. LS was independently associated with lower EQ-5D-5L in all patients with NAFLD but not in those without advanced fibrosis. In the latter, lower EQ-5D-5L was associated with female sex, T2DM, and depression.

CONCLUSIONS: **Patients with NAFLD, even those without advanced fibrosis, have worse HRQoL compared with the general population. In patients with NAFLD without advanced fibrosis, HRQoL is independently associated with non-liver comorbidities but not LS. Multi-disciplinary management is therefore required in NAFLD, irrespective of fibrosis severity.**

Keywords: Cirrhosis; Diabetes; Elastography; Fibrosis; Steatohepatitis.

Nonalcoholic fatty liver disease (NAFLD) prevalence currently ranges between 20% and 35%, depending on the population studied and/or on the diagnostic criteria used.[1] Approximately one-third of the patients with NAFLD may progress to nonalcoholic steatohepatitis (NASH) leading to higher risk for cirrhosis, hepatocellular carcinoma and liver-related death(1). Although NAFLD patients without NASH or advanced fibrosis may carry lower risk of liver-related complications, they still have higher overall mortality risk compared with the general population, mostly due to higher cardiovascular risk.[2]

Apart from clinical signs and symptoms of liver disease, an important health outcome indicator is the disease effect on the health-related quality of life (HRQoL),[3] which focuses on patients' well-being and functioning and can be measured with various utility measures. HRQoL utilities are a crucial tool in public health policy design and health technology assessment, as they are used by health agencies worldwide in informing their recommendations.

HRQoL in patients with NAFLD has been increasingly studied in the past decade,[4] although data in the United Kingdom (UK) population remains scarce. Several generic validated questionnaires, such as the Short Form 36 (SF-36), the EuroQol 5-dimensional (EQ-5D),[4,5] or liver-specific ones, such as the widely validated Chronic Liver Disease questionnaire (CLDQ)[6] and some more recent forms,[7,8]have been used to assess HRQoL in NAFLD. Studies so far have shown that HRQoL is impaired in NAFLD and potentially associated with fibrosis severity,[9,10] obesity, and other metabolic comorbidities.[5,11] However, most data come from clinical trial cohorts, which include highly selected populations and therefore are prone to selection bias. Some data suggest that HRQoL in NAFLD might be worse than that of the general population; however, the comparisons were not adjusted for comorbidities.[12,13] Moreover, it is uncertain if the difference in HRQoL with the general population persists in patients without advanced fibrosis, and whether this impairment is driven by the presence of fibrosis or that of non-liver-related comorbidities.

The primary aim of our study was to assess HRQoL in patients with NAFLD with or without advanced fibrosis and compare this with the UK general population. Secondary aims were to examine the associations of fibrosis severity and metabolic comorbidities with impairments in HRQoL in these patient subgroups.

Methods

Patient Population and Data Collection

This prospective study included patients with NAFLD who were evaluated in 4 UK participating centers and who completed the HRQoL questionnaires between October 2016 and December 2019. The diagnosis of NAFLD was based on histological findings consistent with NAFLD or ultrasonography showing a fatty liver in the absence of other causes of liver disease, based on a negative liver screen and absence of alcohol misuse based on clinical history. Exclusion criteria were alcohol misuse (defined as alcohol intake >20 g/d in women and >30 g/d in men), secondary causes of steatosis (such as steatogenic medication or previous gastrointestinal bypass), or coexistent liver disease of other etiology. The study was approved by a central ethics committee (REC reference 15/WM/0109), and all patients signed an informed consent.

Demographic and clinical information, including age, sex, history of cirrhosis and decompensation, other comorbidities and concomitant medications, smoking, exercise habits, and body mass index (BMI), as well as blood test results at the time of the survey were recorded.

For comparison, we included individuals of the general population from the Health Survey for England (HSE) 2018,[14] which is a large cohort monitoring trends in health and care in adults ≥16 years old, and children aged 0 to 15, from private households in England. In our study, we included adults only, and we excluded those with alcohol misuse, as defined above.

To compare the NAFLD study population with a cohort of the general population with similar baseline

characteristics, we performed propensity-score (PS) matching, according to age, sex, BMI, and presence of type 2 diabetes mellitus (T2DM).

Liver Disease Severity Assessment

All patients with NAFLD had undergone liver transient elastography for the measurement of liver stiffness (LS). For transient elastography measurements, LS values and interquartile range, as well as the probe (M or XL) used were recorded.

For patients with available liver biopsies (233/513; 50%), we recorded NAFLD activity score (NAS score) and the fibrosis stage according to the NASH CRN scoring system. Total NAS score represents the sum of scores for steatosis, lobular inflammation, and ballooning, and ranges from 0 to 8.[15]

Cirrhosis was defined as either fibrosis stage (F) = 4 in patients with available liver biopsy or LS >15 kPa and either nodular liver or splenomegaly on ultrasound or platelet count <100,000/mm^3. Among non-cirrhotic patients, advanced fibrosis was defined as either F3 fibrosis stage in patients with available liver biopsy or LS >8 kPa.[16]

In the HSE cohort, there were no data on the presence or severity of liver disease.

HRQoL Assessment

All included patients completed the survey questionnaire, which was anonymized and consisted of the EQ-5D questionnaire[17] as well as the Chronic Liver Disease questionnaire (CLDQ).[6]

EQ-5D is a widely used, standardized, preference-based instrument for measuring generic health status.[17]The EQ-5D has 2 components: the descriptive system and the visual analog scale (VAS). The descriptive system includes 5 elements: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these can be scored by the patient using 5 levels (5L) of severity: no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to perform any activities.[18]

From the 5 domains, we calculated the EQ-5D-5L utility index, as recommended by the recent NICE position statement,[19] using the "EQ-5D-5L Crosswalk Index Value Calculator." The utility index EQ-5D-5L is a score on a −0.594 to 1 scale with negative scores indicating states worse than dead and 1 being the best possible health imaginable.[18,19]

Furthermore, the EQ VAS score records the patient's self-rated health on a vertical scale from 0 to 100. A score of 100 means 'the best health you can imagine' and 0 'the worst health you can imagine.'[18,19]

Our study participants also completed the CLDQ, which is a liver disease-specific questionnaire. The CLDQ included 29 items on a 7-point Likert scale ranging from 1 (all of the time) to 7 (none of the time), indicating the frequency of clinical symptoms and emotions in the last 2 weeks from the completion of the questionnaire. CLDQ generates 6 subscale-domain scores (abdominal symptoms, fatigue, systemic symptoms, activity, emotional functioning, worry) and a CLDQ overall score.[6]

A minimal clinically important difference of 0.5 in the CLDQ overall score is considered clinically relevant.[6,11]

In the HSE survey, only the EQ-5D-5L was available for all patients, and therefore, this tool was used to compare HRQoL between our patients with NAFLD and the general population sub-cohort.[14]

Statistical Analysis

Descriptive statistics were computed for all variables. Parametric and non-parametric quantitative variables were presented by their mean values ± standard

What you need to know

Background

Health-related quality of life (HRQoL) is impaired in patients with advanced chronic liver disease. We are still not certain whether HRQoL is impaired in patients with nonalcoholic fatty liver disease (NAFLD) who do not have advanced fibrosis. In this study, we evaluated HRQoL in patients with different stages of NAFLD in comparison with the general population of the United Kingdom (UK).

Findings

Our data show that HRQoL, as evaluated with different validated tools (the widely used EuroQol 5-D-5L utility index and the liver disease-specific Chronic Liver Disease Questionnaire [CLDQ] score), is worse in patients with NAFLD compared with the general population of the UK, and this impairment is present even in those who do not have advanced fibrosis. Among those patients with NAFLD who do not have advanced fibrosis, risk factors of HRQoL impairment were non-liver-related, including female sex, type 2 diabetes, and depression.

Implications for patient care

Multidisciplinary clinical care models are warranted in people with NAFLD, as they have impairment in their quality of life compared with the general population that is not necessarily associated with liver-related factors, particularly in those who do not have advanced fibrosis. In this study, we provide utility values for different stages of NAFLD that can be used to inform health economic modeling when considering the costeffectiveness of therapeutic interventions.

deviation or median values (interquartile range), respectively. Comparisons between 2 patient groups were performed by t test or non-parametric Mann-Whitney test. The corrected χ^2 or 2-sided Fisher exact test was used to test for association between 2 categorical variables.

The PS was determined from the fit of a multivariable logistic regression model including the parameters reported above, and 1:1 PS-matching with the precision of 1 decimal digit was applied.

Univariate or multivariate linear regression models were used to examine association between patient characteristics and HRQoL indices. All data were analyzed using the statistical package SPSS (version 27.0; IBM Corp, Armonk, NY) and R version 4.1.2 (November 2021). A 2-tailed P-value $< .05$ was considered statistically significant.

Results

Basic Characteristics of the Study Population

The study included 513 patients with NAFLD with complete data. Their mean age was 59 ±13 years, and 295 (58%) of them were males. Mean BMI was 33.6 ± 7.1 kg/m^2, and the majority (67%) were obese (BMI ≥30 kg/m^2).

Of the 513 patients, 147 (28%) had cirrhosis according to the study definition. The diagnosis of cirrhosis was based on liver biopsy in 66 (45%) of the 147 patients with cirrhosis. Among the rest of the patients (n = 366), 117 had NAFLD with advanced fibrosis as defined above, whereas 249 did not have advanced fibrosis. The most common non-liver comorbidities were hypertension (58%), T2DM (49%), dyslipidemia (44%), and depression (15%). Basic characteristics of all patients with NAFLD and those without advanced fibrosis are presented in Table 1.

The general population sub-cohort (n = 5734) who met the inclusion criteria (adults >16 years and no alcohol misuse) differed significantly from the study patients with NAFLD in relation to age and sex distribution, as well as BMI and presence of T2DM. After 1:1 PS-matching, the 2 groups were adjusted to the best extent (Supplementary Table 1).

Comparison of HRQoL Between Patients With NAFLD and the UK General Population

EQ-5D-5L index was significantly lower in patients with NAFLD compared with the PS-matched controls (0.768 ± 0.273 vs 0.841 ± 0.194; $P < .001$) (Figure 1). Importantly, the difference remained significant when only patients with NAFLD without advanced fibrosis were compared (0.797 ± 0.243 vs 0.841 ± 0.194; $P = .024$) (Supplementary Table 1).

Table 1. Basic Characteristics for Study Patients

	All patients with NAFLD (n = 513)	Patients with NAFLD without advanced fibrosis (n = 249)
Demographics		
Center		
London	237 (46)	164 (66)
Nottingham	104 (20)	36 (15)
Cambridge	102 (20)	23 (9)
Oxford	70 (14)	26 (10)
Age, years	59 ± 13	56 ± 13
Male gender	295 (58)	152 (62)
BMI, kg/m^2	33.6 ± 7.1	32.5 ± 6.3
Smoking	36 (7)	14 (6)
Degree of professional qualification	225 (44)	132 (53)
Liver disease severity		
Cirrhosis	147 (28)	0
Advanced fibrosis	117 (23)	0
Non-advanced fibrosis	249 (49)	249 (100)
Non-liver comorbidities		
Type 2 diabetes	254 (50)	86 (35)
Hypertension	295 (58)	127 (51)
Dyslipidemia	45 (9)	24 (10)
Cardiovascular disease	41 (8)	12 (5)
Depression	76 (15)	38 (15)
Osteoarthritis	45 (9)	13 (5)
Medications used		
Statins	234 (46)	105 (42)
Anti-hypertensive	258 (50)	111 (45)
Metformin	201 (39.)	67 (27)
Liraglutide	15 (2.9)	2 (0.8)
Gliclazide	58 (11)	20 (8)
Antidepressants	98 (19)	45 (18)
Vitamin D	42 (8)	9 (4)

Note: Data are presented as number (%) or mean ± standard deviation.
BMI, Body mass index; NAFLD, nonalcoholic fatty liver disease.

Because the difference in the prevalence of diabetes was significant in the 466 pairs of PS-matched individuals even after optimal 1:1 matching ($P = .018$) (Supplementary Table 1), we performed a multivariate linear regression analysis to assess whether the presence of NAFLD and diabetes affected EQ-5D-5L. Indeed, we found that lower EQ-5D-5L values were independently associated with the presence of NAFLD (B, −0.67; 95% confidence interval [CI], −0.097 to −0.037; $P < .001$) and the presence of T2DM (B, −0.74; 95% CI, −0.104 to −0.044; $P < .001$). Moreover, when the multivariate model included the severity of NAFLD (ie, cirrhosis vs advanced fibrosis vs no advanced fibrosis vs general population) and the presence of T2DM, NAFLD severity (B, −0.036; 95% CI, −0.050 to −0.022; $P < .001$) and the presence of T2DM (B, −0.73; 95% CI, −0.103 to −0.043; $P < .001$) were independently associated with impaired EQ-5D-5L.

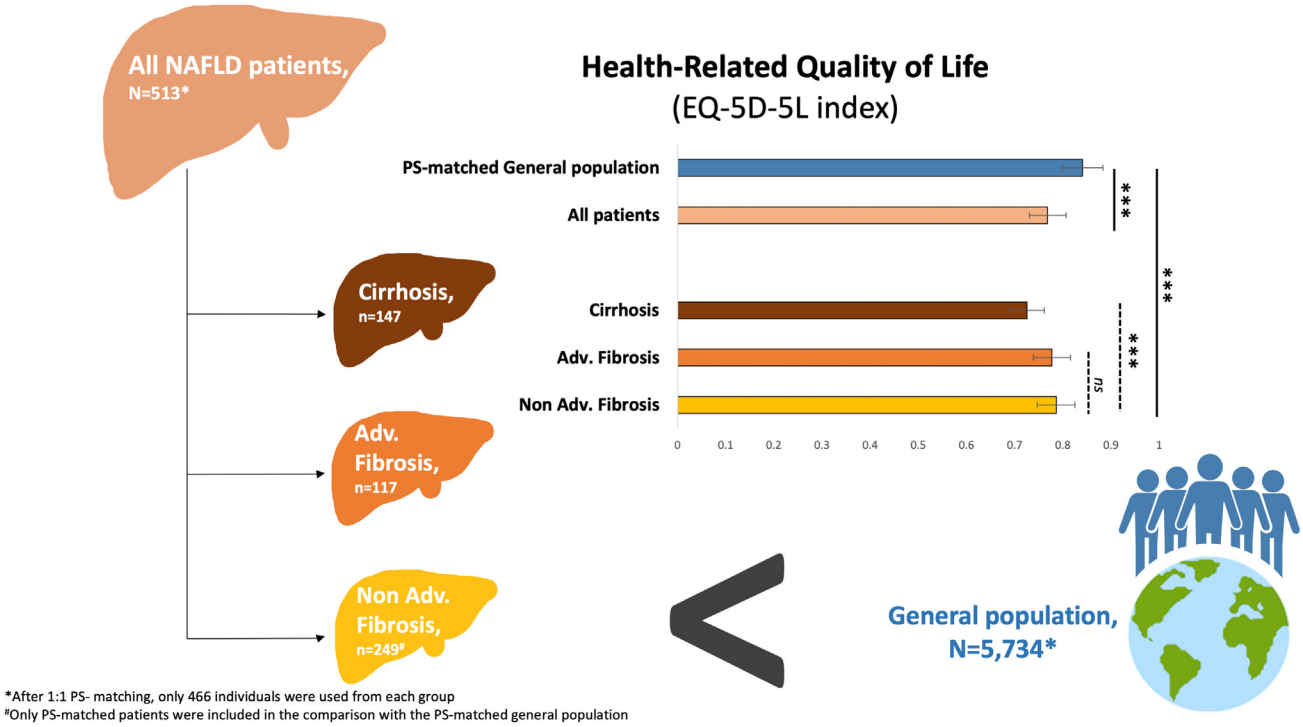

Figure 1. Presentation of study patient groups and comparisons EQ-5D-5L index.

HRQoL in Patients With NAFLD According to the Presence of Advanced Fibrosis or Cirrhosis

Among patients with NAFLD, there was no difference in any of the HRQoL indices between those with (n = 117) or without (n = 249) advanced fibrosis (EQ-5D-5L, 0.777 ± 0.263 vs 0.786 ± 0.267; $P = .570$; EQ VAS, 69.60 ± 20.70 vs 71.84 ± 18.26; $P = .339$; CLDQ, 5.041 ± 1.315 vs 5.083 ± 1.323; $P = .630$) (Table 2).

However, all indices were significantly lower in cirrhotic (n = 147) compared with non-cirrhotic (n = 366) patients (Supplementary Table 2).

Therefore, there was significant HRQoL impairment in all stages of NAFLD.

Table 2. Comparisons of EQ-5D Indices and CLDQ Score Between Patients With NAFLD With and Without Advanced Fibrosis

	Patients with NAFLD		
HRQoL score	With advanced fibrosis (n = 117)	Without advanced fibrosis (n = 249)	*P*-value
EQ 5D-5L	0.777 ± 0.263	0.786 ± 0.267	.570
EQ VAS	69.60 ± 20.70	71.84 ± 18.26	.339
CLDQ score overall	5.041 ± 1.315	5.083 ± 1.323	.630
Abdominal symptoms	5.203 ± 1 .719	5.161 ± 1.672	.936
Fatigue	4.206 ± 1.454	4.497 ± 1.559	.789
Systemic symptoms	5.101 ± 1.404	5.058 ± 1.425	.949
Activity	5.304 ± 1.464	5.399 ± 1.524	.489
Emotional function	5.016 ± 1.461	5.014 ± 1.479	.869
Worry	5.161 ± 1.530	5.373 ± 1.547	.122

Note: Data are presented as mean ± standard deviation.
CLDQ, Chronic Liver Disease Questionnaire; EQ-5D, EuroQol 5-dimensional questionnaire; HRQoL, health-related quality of life; NAFLD, nonalcoholic fatty liver disease; VAS, visual analog scale.

Factors Associated With HRQoL Indices

Among patients with NAFLD (n = 513), higher LS values were significantly associated with lower scores in all HRQoL indices (EQ-5D-5L, B, −0.006; 95% CI, −0.009 to −0.003; $P < .001$; EQ VAS, B, −0.320; 95% CI, −0.523 to −0.135; $P = .001$; CLDQ score, B, −0.026; 95% CI, −0.039 to −0.013; $P < .001$). For patients with available histology, NAS score or the fibrosis stage were not associated with HRQoL scores (Supplementary Table 3). In particular, in patients with NAFLD without advanced fibrosis, LS was not significantly associated with any of the HRQoL indices (Supplementary Table 3). This implies that fibrosis severity drives the impairment of HRQoL once the patients develop advanced fibrosis.

To understand if the negative association of LS with HRQoL was affected by specific patient characteristics or non-liver-related comorbidities, we examined a multivariate linear regression model including LS, age, sex, BMI, and the 4 most common non-liver comorbidities (hypertension, T2DM, dyslipidemia, and depression) (Table 3).

EQ-5D-5L was independently associated with LS (B, −0.004; 95% CI, −0.007 to −0.001; $P = .005$), T2DM (EQ-5D-5L: B, −0.092; 95% CI, −0.146 to −0.038; $P = .001$), and depression (EQ-5D-5L: B, −0.215; 95% CI, −0.285 to −0.145; $P < .001$) in all patients with NAFLD. When the analysis was restricted to patients without advanced fibrosis, LS did not remain an independent predictor of lower EQ-5D-5L, but all other factors were. Similarly, EQ-VAS and CLDQ scores did not remain significantly associated with LS when only patients without advanced fibrosis were included.

Sensitivity analysis in non-cirrhotic patients (including 117 with and 249 without advanced fibrosis) are presented in Supplementary Tables 4 and 5. In brief, LS was independently associated with lower values of all 3 HRQoL indices in this subgroup, suggesting that increasing LS values affect HRQoL mostly in the more advanced stages of the NAFLD spectrum, but LS does no longer contribute to HRQoL impairment in patients with mild stages of the disease.

Finally, we also examined the most common co-medications received by the patients as factors

Table 3. Multivariate Linear Regression Models Assessing the Association of EQ-5D Indices and CLDQ Scores With Patient Characteristics

	All patients with NAFLD (n = 513)		Patients with NAFLD without advanced fibrosis (n = 249)	
	B (95% CI)	*P*-value	B (95% CI)	*P*-value
EQ-5D-5L				
LS, kPa	−0.004 (−0.007 to −0.001)	**.005**	−0.004 (−0.017 to 0.009)	.470
Age at survey, per year	0.001 (−0.001 to 0.003)	.396	0.002 (−0.001 to 0.005)	.175
Sex, male vs female	−0.048 (−0.098 to 0.001)	.056	−0.080 (−0.152 to −0.008)	**.032**
BMI, per kg/m^2	−0.003 (−0.006 to 0.001)	.129	0.000 (−0.006 to 0.006)	.986
Hypertension, yes vs no	−0.011 (−0.067 to 0.046)	.713	−0.004 (−0.086 to 0.077)	.880
T2DM, yes vs no	−0.092 (−0.146 to −0.038)	**.001**	−0.138 (−0.219 to −0.057)	**< .001**
Dyslipidemia, yes vs no	0.004 (−0.051 to 0.058)	.893	0.042 (−0.039 to 0.123)	.316
Depression, yes vs no	−0.215 (−0.285 to −0.145)	**< .001**	−0.156 (−0.252 to −0.059)	**.003**
EQ-5D VAS				
LS, kPa	−0.220 (−0.416 to −0.024)	**.028**	−0.221(−1.096 to −0.654)	.661
Age at survey, per year	0.190 (0.033 to 0.347)	**.018**	0.168 (−0.028 to 0.365)	.110
Sex, male vs female	−5.487 (−9.145 to −1.829)	**.003**	−8.107 (−12.894 to −3.320)	**.001**
BMI, per kg/m^2	−0.378 (−0.648 to −0.109)	**.006**	−0.407 (−0.822 to 0.08)	**.048**
Hypertension, yes vs no	0.007 (−4.151 to 4.165)	.997	3.673 (−9.125 to 1.661)	.192
T2DM, yes vs no	−3.437 (−7.395 to 0.521)	.089	−3.732 (−9.125 to 1.661)	.172
Dyslipidemia, yes vs no	1.163 (−2.852 to 5.177)	.569	1.921 (−3.452 to 7.293)	.482
Depression, yes vs no	−14.793 (−19.915 to −9.670)	**< .001**	−11.976(−18.394,−5.559)	**< .001**
CLDQ score				
LS, per kPa	−0.020 (−0.033 to −0.007)	**.002**	−0.013 (−0.075 to 0.049)	.684
Age, per year	0.008 (−0.003 to 0.018)	.139	0.007 (−0.007 to 0.021)	.322
Sex, male vs female	−0.532 (−0.769 to −0.295)	**< .001**	−0.589 (−0.930 to −0.248)	**.001**
BMI, per kg/m^2	−0.004 (−0.021 to 0.014)	.688	0.010 (−0.020 to 0.039)	.517
Hypertension, yes vs no	0.090 (−0.180 to 0.359)	.514	0.203 (−0.182 to 0.587)	.300
T2DM, yes vs no	−0.305 (−0.562 to −0.049)	**.020**	−0.391(−0.775 to −0.007)	**.046**
Dyslipidemia, yes vs no	0.071 (−0.190 to 0.331)	.594	0.256 (−0.126 to 0.639)	.188
Depression, yes vs no	−1.240 (−1.571 to −0.908)	**< .001**	−1.234 (−1.691 to −0.777)	**< .001**

Note: Boldface *P* values indicate statistical significance.
BMI, Body mass index; CI, confidence interval; CLDQ, Chronic Liver Disease Questionnaire; EQ-5D, EuroQol 5-dimensional questionnaire; LS, liver stiffness; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; VAS, visual analog scale.

affecting HRQoL and among them, the use of metformin, gliclazide, antidepressants, and vitamin D supplements were significantly associated with lower EQ-5D-5L, but statins, anti-hypertensive treatment, or liraglutide were not (Supplementary Table 6). The results were similar when we included all patients with NAFLD in the analysis (Supplementary Table 6).

Discussion

In this real-world UK NAFLD cohort, we showed that quality of life was significantly lower in patients with NAFLD compared with PS-matched controls from a general population cohort. More importantly, the impairment in HRQoL remained significant even in patients with NAFLD who did not have advanced fibrosis. Along these lines, the presence and increasing severity of NAFLD was an independent factor associated with impaired HRQoL, in addition to T2DM. These findings are crucial for guiding public health policies and health economic modelling for reimbursement of the upcoming pharmacological treatments in NAFLD, since until now, HRQoL data originated mostly from clinical trial cohorts, which represent a highly selective patient population.

Our findings show that patients with and without advanced fibrosis had similar HRQoL scores, which is in line with a recent study,[11] and that even those without advanced fibrosis have worse HRQoL compared with the general population. In a recent large global study from various geographical regions, HRQoL and patient-reported outcomes were lower in patients with NAFLD compared with the local general population, but these were not matched for comorbidities, whereas the severity of NAFLD was not reported.[13] Moreover, a smaller recent study suggested that HRQoL evaluated by SF-36, a different utility index than ours, may be worse in patients without advanced fibrosis than in the general population obtained from published literature.[12] Our findings are more robust, as we included patients with milder NAFLD (LS $<$8 KPa instead of $<$12 KPa for advanced fibrosis) and a propensity-matched sample of the general population.

Interestingly, when only patients with NAFLD without advanced fibrosis were included in the analysis, there was no association between LS and any of the HRQoL indices, suggesting no effect of milder fibrosis stages in the worsening HRQoL. There is still uncertainty whether this impairment is due to the presence of non-liver comorbidities or if the presence of NAFLD per se is an additional contributing factor over and above these comorbidities. A recent study has shown that, in patients with NAFLD without advanced fibrosis,[12] body fat content is associated with the HRQoL impairment. In line with this, it was shown that weight loss improved HRQoL in patients with NAFLD.[20] According to our data, impaired HRQoL in the subgroup of patients without advanced fibrosis was associated with non-liver comorbidities such as depression and diabetes.

Moreover, poor understanding of the disease and lack of information regarding disease progression and management, as well as insufficient patient support from the physicians' side, might be some of the reasons.[21,22] The fact that the diagnosis of NAFLD is usually incidental and its symptoms remain concealed for a long period of time adds more concern to the patients, who are usually already vigilant, because they commonly present other severe comorbidities, such as diabetes, obesity, and cardiovascular disease.[21] Finally, the bidirectional association between metabolic syndrome and mental health issues is present in patients with NAFLD, as they commonly suffer from anxiety, depression, and chronic stress that may lead to worse HRQoL.[23]

Our study strengths include a representation of the whole NAFLD spectrum, the use of both a liver-specific (CLDQ score) and a general HRQoL tool (EQ5D-5L), as well as comparison with a large PS-matched general UK population cohort. Moreover, our real-world data reinforce the findings of previous studies on HRQoL in NAFLD cohorts from therapeutic clinical trials. It can be argued that such studies have diagnosed the stages of NAFLD with better accuracy but also included patients with more severe liver disease and thus might have overestimated the impairment in HRQoL. Our study provides utility values for any NAFLD fibrosis stage in comparison to the general population and reflects more accurately HRQoL in a real-world setting, offering valuable insight for actual health economic models.

Yet, there are some limitations to acknowledge. Firstly, the proportion of patients with NAFLD with cirrhosis was relatively high (28%), as our NAFLD study population was patients seen in tertiary UK hospitals with specialized NAFLD clinics. Secondly, the HSE general population cohort that we used as comparator lacked data with regards to liver disease history, imaging of the upper abdomen, or adequate details to calculate noninvasive NAFLD diagnostic biomarkers, such as the fatty liver index. Therefore, the presence of NAFLD in this general population cohort could not be excluded. However, the latter limitation could only weaken the probability of revealing significant HRQoL differences between our patients with NAFLD and controls. Finally, we have not used some new scores that have been recently developed for the evaluation of HRQoL specifically in NAFLD,[7,8] as our study preceded their development. However, there is limited external validation of those scores, and the tools we used are widely implemented in clinical practice.

Overall, we showed that patients with NAFLD have worse HRQoL compared with the general population independently of the severity of liver fibrosis. Importantly, it seems that non-liver-related comorbidities drive the impairment in HRQoL in patients with NAFLD without advanced fibrosis. Although future research is required to further reveal the exact factors driving impaired HRQoL in this patient subgroup, these results suggest that patients with NAFLD need effective

multi-disciplinary management irrespective of their fibrosis severity.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.04.018.

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Conflicts of interest
The authors disclose no conflicts.

Supplementary Table 1. Comparison of basic characteristics of the general population individuals and patients with NAFLD

Variables	General population (n = 5734)	All patients with NAFLD (n = 513)	*P*-value	General population: PS-matched (n = 466)	Patients with NAFLD: PS matched (n = 466)	*P*-value
Male sex	2401 (42)	293 (57)	**< .001**	239 (51)	262 (56)	.074
Age groups, years			**< .001**			.591
16–24	499 (9)	6 (1)		4 (1)	6 (1)	
25–34	778 (14)	16 (3)		35 (8)	12 (3)	
35–44	895 (16)	41 (8)		37 (8)	38 (8)	
45–54	921 (16)	107 (21)		82 (18)	97 (21)	
55–64	872 (15)	147 (29)		101 (22)	135 (29)	
65–74	950 (17)	148 (29)		124 (27)	133 (29)	
75+ years	819 (14)	46 (9)		83 (9)	45 (5)	
BMI, kg/m^2	25.6 [9]	32.4 [8.7]	**< .001**	31.9 [8.5]	32.3 [8.7]	.221
T2DM	249 (10[a])	259 (51)	**< .001**	198 (43)	231 (50)	**.018**
EQ-5D-5L	0.861±0.205	0.768±0.273	**< .001**	0.841±0.194	0.768±0.273	**< .001**

Note: Data are presented as number (%), mean ± standard deviation, or median [interquartile range].
Note: Boldface *P* values indicate statistical significance.
BMI, Body mass index; EQ-5D, EuroQol 5-dimensional questionnaire; NAFLD, nonalcoholic fatty liver disease; PS, propensity score; T2DM, type 2 diabetes mellitus.
[a]Patients with available data.

Supplementary Table 2. Comparisons of EQ-5D Indexes and CLDQ Domains and Overall Score Between Patients With NAFLD With (n = 147) and Without Cirrhosis (n = 366)

	Patients with NAFLD		
HrQoL score	With cirrhosis	Without cirrhosis	*P*-value
EQ-5D			
EQ 5D-5L	0.725 ± 0.285	0.787 ± 0.264	**.032**
EQ VAS	67.17 ± 21.42	71.36 ± 19.08	**.046**
CLDQ			
Abdominal symptoms (AB)	4.988 ± 1.681	5.197 ±1.685	.245
Fatigue (FA)	3.960 ± 1.415	4.518 ± 1.532	**< .001**
Systemic symptoms (SY)	4.412 ± 1.346	5.092 ± 1.417	**< .001**
Activity (AC)	4.882 ± 1.445	5.391 ± 1.505	**< .001**
Emotional function (EM)	4.775 ± 1.421	5.039 ± 1.477	.072
Worry (WO)	5.012 ± 1.621	5.315 ± 1.543	.061
CLDQ overall	4.673 ± 1.216	5.092 ± 1.323	**.001**

CLDQ, Chronic Liver Disease Questionnaire; EQ-5D, EuroQol 5-dimensional questionnaire; HRQoL, health-realated quality of life; NAFLD, nonalcoholic fatty liver disease; VAS, visual analog scale.

Supplementary Table 3. Univariate Linear Regression Analysis Assessing EQ-5D Indices and CLDQ Score With LS or Histological Features in All Patients With NAFLD and Those Without Advanced Fibrosis (Fibrosis Stage ≤2 and/or LS <8 kPa)

	All patients with NAFLD (n = 513)		Patients with NAFLD without advanced fibrosis (n = 249)	
	B (95% CI)	*P*-value	B (95% CI)	*P*-value
EQ-5D 5L				
LS	−0.006 (−0.009 to −0.003)	**< .001**	−0.010 (−0.023 to 0.002)	.096
NAS score	−0.011 (−0.045 to 0.022)	.501	−0.042 (−0.099 to 0.015)	.150
Fibrosis stage	−0.013 (−0.046 to 0.019)	.419	−0.031 (−0.135 to 0.072)	.549
EQ-5D VAS				
LS	−0.320 (−0.523 to −0.135)	**.001**	−0.616 (−1.467 to 0.235)	.155
NAS score	0.441 (1.946 to 2.829)	.716	−0.827 (−4.431 to 2.276)	.647
Fibrosis stage	−0.296 (−2.517 to 1.926)	.793	−0.188 (−6.646 to 6.270)	.954
CLDQ score				
LS	−0.026 (−0.039 to −0.013)	**< .001**	−0.023 (−0.085 to 0.039)	.465
NAS score	−0.049 (−0.201 to 0.102)	.520	−0.099 (−0.351 to 0.153)	.435
Fibrosis stage	−0.061 (−0.208 to 0.086)	.417	0.083 (−0.407 to 0.573)	.737

Note: Boldface *P* values indicate statistical significance.
CI, Confidence interval; CLDQ, Chronic Liver Disease Questionnaire; EQ-5D, EuroQol 5-dimensional questionnaire; LS, liver stiffness; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; VAS, visual analog scale.

Supplementary Table 4. Univariate Linear Regression Analysis Assessing EQ-5D Indices and CLDQ Score With LS or Histological Features in Patients With NAFLD After Excluding Those With Cirrhosis

	B (95% CI)	*P*-value
EQ-5D 5L		
LS, kPa	−0.009 (−0.015 to −0.004)	**< .001**
NAS score	−0.012 (−0.049 to 0.024)	.497
Fibrosis stage	−0.002 (−0.047 to 0.043)	.928
EQ-5D VAS		
LS, kPa	−0.700 (−1.079 to −0.321)	**< .001**
NAS score	0.319 (−2.359 to 2.998)	.814
Fibrosis stage	−0.409 (−3.497 to 2.679)	.794
CLDQ score		
LS, kPa	−0.031 (−0.057 to −0.004)	**.023**
NAS score	−0.066 (−0.237 to 0.104)	.441
Fibrosis stage	0.024 (−0.189 to 0.236)	.824

Note: Boldface *P* values indicate statistical significance.
CI, Confidence interval; CLDQ, Chronic Liver Disease Questionnaire; EQ-5D, EuroQol 5-dimensional questionnaire; LS, liver stiffness; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; VAS, visual analog scale.

Supplementary Table 5. Multivariate Linear Regression Models Assessing the Association of EQ-5D Indices and CLDQ Scores With Age, Sex, and Comorbidities in Patients With NAFLD After Excluding Those With Cirrhosis

	B (95% CI)	*P*-value
EQ-5D 5L		
LS, kPa	−0.005 (−0.011 to 0.000)	**.052**
Age at survey, per year	0.001 (−0.001 to 0.004)	.332
Sex, male vs female	−0.057 (−0.113 to 0.000)	**.049**
BMI, per kg/m^2	−0.002 (−0.006 to 0.002)	.411
Hypertension, yes vs no	0.015 (−0.079 to 0.049)	.641
T2DM, yes vs no	−0.107 (−0.169 to −0.046)	**.001**
Dyslipidemia, yes vs no	0.018 (−0.046 to 0.083)	.579
Depression, yes vs no	−0.175 (−0.253 to −0.096)	**< .001**
EQ-5D VAS		
LS, kPa	−0.422 (−0.798 to −0.045)	**.028**
Age at survey, per year	0.178 (0.004 to 0.351)	.045
Sex, male vs female	−6.996 (−10.982 to −3.011)	**.001**
BMI, per kg/m^2	0.336 (−0.621 to 0.051)	.021
Hypertension, yes vs no	1.027 (−3.483 to 5.537)	.654
T2DM, yes vs no	−3.800 (−8.114 to −0.513)	.084
Dyslipidemia, yes vs no	1.329 (−3.206 to 5.864)	.565
Depression, yes vs no	−15.043 (−20.583 to −0.504)	**< .001**
CLDQ score		
LS, kPa	−0.015 (−0.041 to −0.010)	.242
Age at survey, per year	0.006 (−0.006 to 0.018)	.309
Sex, male vs female	−0.568 (−0.840 to −0.296)	**< .001**
BMI, per kg/m^2	0.001 (−0.018 to 0.021)	.908
Hypertension, yes vs no	0.138 (−0.170 to 0.445)	.379
T2DM, yes vs no	−0.312 (−0.606 to −0.018)	**.038**
Dyslipidemia, yes vs no	0.122 (−0.187 to 0.431)	.438
Depression, yes vs no	−1.268 (−1.646 to −0.890)	**< .001**

Note: Boldface *P* values indicate statistical significance.
BMI, Body mass index; CI, confidence interval; CLDQ, Chronic Liver Disease Questionnaire; EQ-5D, EuroQol 5-dimensional questionnaire; LS, liver stiffness; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; VAS, visual analog scale.

Supplementary Table 6. Association of EQ-5D-5L With Co-medications in All Patients With NAFLD and Those Without Advanced Fibrosis

	All patients with NAFLD (n = 513)		Patients with NAFLD without advanced fibrosis (n = 249)	
	B (95% CI)	*P*-value	B (95% CI)	*P*-value
Medications, yes vs no				
Statins	−0.02 (−0.07 to 0.03)	.459	−0.03 (0.10 to 0.05)	.465
Anti-hypertensive	−0.04 (−0.09 to 0.01)	.102	−0.03 (−0.10 to 0.04)	.416
Metformin	−0.10 (−0.16 to −0.05)	< .001	−0.11 (−0.19 to −0.03)	.007
Liraglutide	−0.11 (−0.26 to 0.05)	.169	−0.26 (−0.66 to 0.15)	.209
Gliclazide	−0.03 (−0.12 to 0.05)	.433	−0.14 (−0.27 to −0.01)	.037
Antidepressants	−0.25 (−0.32 to −0.19)	< .001	−0.22 (−0.31 to −0.13)	< .001
Vitamin D	−0.16 (−0.26 to −0.66)	.001	−0.31 (−0.50 to −0.12)	.002

CI, Confidence interval; EQ-5D, EuroQol 5-dimensional questionnaire; LS, liver stiffness; NAFLD, nonalcoholic fatty liver disease.