The impact of stigma on quality of life and liver disease burden among patients with nonalcoholic fatty liver disease
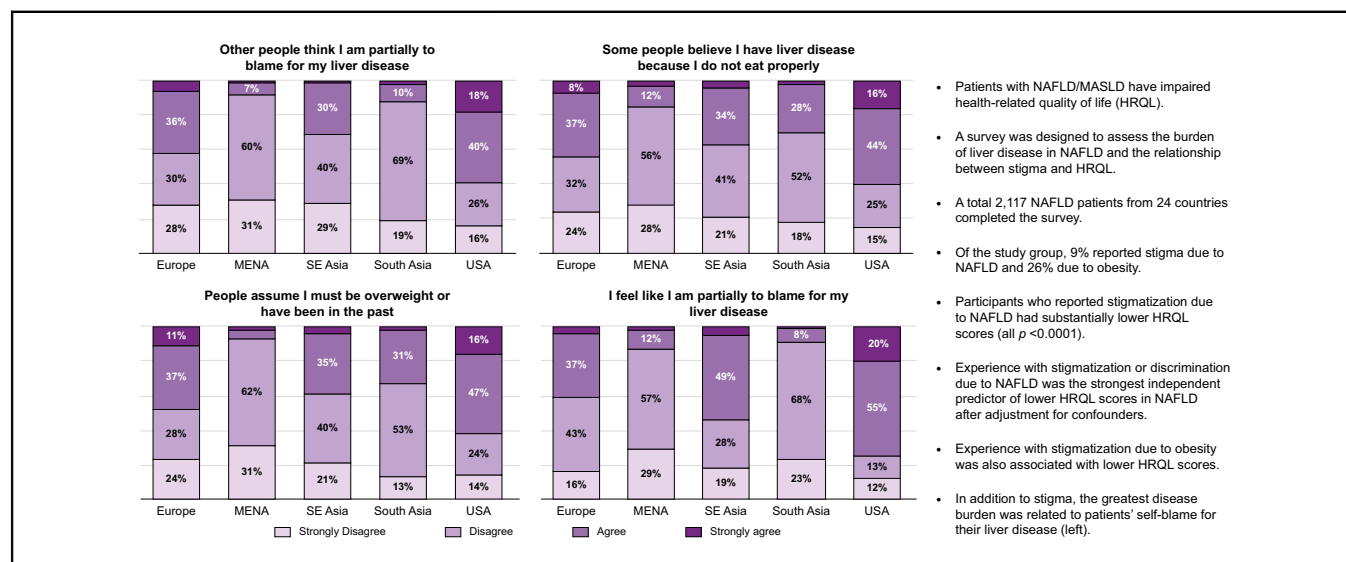
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Graphical abstract

Graphical abstract charts. Columns grouped by region: Europe, MENA, SE Asia, South Asia, USA. Legend: Strongly Disagree, Disagree, Agree, Strongly agree.

Other people think I am partially to blame for my liver disease
- Europe: 28%, 30%, 36%, (top)
- MENA: 31%, 60%, 7%
- SE Asia: 29%, 40%, 30%
- South Asia: 19%, 69%, 10%
- USA: 16%, 26%, 40%, 18%

Some people believe I have liver disease because I do not eat properly
- Europe: 24%, 32%, 37%, 8%
- MENA: 28%, 56%, 12%
- SE Asia: 21%, 41%, 34%
- South Asia: 18%, 52%, 28%
- USA: 15%, 25%, 44%, 16%

People assume I must be overweight or have been in the past
- Europe: 24%, 28%, 37%, 11%
- MENA: 31%, 62%
- SE Asia: 21%, 40%, 35%
- South Asia: 13%, 53%, 31%
- USA: 14%, 24%, 47%, 16%

I feel like I am partially to blame for my liver disease
- Europe: 16%, 43%, 37%, (top)
- MENA: 29%, 57%, 12%
- SE Asia: 19%, 28%, 49%
- South Asia: 23%, 68%, 8%
- USA: 12%, 13%, 55%, 20%

- Patients with NAFLD/MASLD have impaired health-related quality of life (HRQL).
- A survey was designed to assess the burden of liver disease in NAFLD and the relationship between stigma and HRQL.
- A total 2,117 NAFLD patients from 24 countries completed the survey.
- Of the study group, 9% reported stigma due to NAFLD and 26% due to obesity.
- Participants who reported stigmatization due to NAFLD had substantially lower HRQL scores (all *p* <0.0001).
- Experience with stigmatization or discrimination due to NAFLD was the strongest independent predictor of lower HRQL scores in NAFLD after adjustment for confounders.
- Experience with stigmatization due to obesity was also associated with lower HRQL scores.
- In addition to stigma, the greatest disease burden was related to patients' self-blame for their liver disease (left).

Highlights

- A survey of stigma and disease burden was completed by patients with NAFLD/MASLD.
- Stigmatization due to liver disease was strongly associated with impaired quality of life.
- Stigmatization due to obesity was also associated with lower quality of life scores.
- The greatest disease burden was related to patients' self-blame for their liver disease.
- Addressing disease stigma may improve patients' well-being and self-efficacy.

Impact and implications

Patients with nonalcoholic fatty liver disease (NAFLD), recently renamed metabolic dysfunction-associated steatotic liver disease (MASLD), may experience impaired health-related quality of life and stigmatization. Using a specifically designed survey, we found that stigmatization of patients with NAFLD, whether it is caused by obesity or the liver disease *per se*, is strongly and independently associated with a substantial impairment of their quality of life. Physicians treating patients with NAFLD should be aware of the profound implications of stigma, the high prevalence of self-blame in the context of this disease burden, and that providers' perception may not adequately reflect patients' perspective and experience with the disease.

The impact of stigma on quality of life and liver disease burden among patients with nonalcoholic fatty liver disease

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Background & Aims: Patients with nonalcoholic fatty liver disease (NAFLD)/metabolic dysfunction-associated steatotic liver disease (MASLD) face a multifaceted disease burden which includes impaired health-related quality of life (HRQL) and potential stigmatization. We aimed to assess the burden of liver disease in patients with NAFLD and the relationship between experience of stigma and HRQL.

Methods: Members of the Global NASH Council created a survey about disease burden in NAFLD. Participants completed a 35-item questionnaire to assess liver disease burden (LDB) (seven domains), the 36-item CLDQ-NASH (six domains) survey to assess HRQL and reported their experience with stigmatization and discrimination.

Results: A total of 2,117 patients with NAFLD from 24 countries completed the LDB survey (48% Middle East and North Africa, 18% Europe, 16% USA, 18% Asia) and 778 competed CLDQ-NASH. Of the study group, 9% reported stigma due to NAFLD and 26% due to obesity. Participants who reported stigmatization due to NAFLD had substantially lower CLDQ-NASH scores (all p <0.0001). In multivariate analyses, experience with stigmatization or discrimination due to NAFLD was the strongest independent predictor of lower HRQL scores (beta from -5% to -8% of score range size, p <0.02). Experience with stigmatization due to obesity was associated with lower Activity, Emotional Health, Fatigue, and Worry domain scores, and being uncomfortable with the term "fatty liver disease" with lower Emotional Health scores (all p <0.05). In addition to stigma, the greatest disease burden as assessed by LDB was related to patients' self-blame for their liver disease.

Conclusions: Stigmatization of patients with NAFLD, whether it is caused by obesity or NAFLD, is strongly and independently associated with a substantial impairment of their HRQL. Self-blame is an important part of disease burden among patients with NAFLD.

Impact and implications: Patients with nonalcoholic fatty liver disease (NAFLD), recently renamed metabolic dysfunction-associated steatotic liver disease (MASLD), may experience impaired health-related quality of life and stigmatization. Using a specifically designed survey, we found that stigmatization of patients with NAFLD, whether it is caused by obesity or the liver disease *per se*, is strongly and independently associated with a substantial impairment of their quality of life. Physicians treating patients with NAFLD should be aware of the profound implications of stigma, the high prevalence of self-blame in the context of this disease burden, and that providers' perception may not adequately reflect patients' perspective and experience with the disease.

Introduction

Steatotic liver disease, formerly known as fatty liver disease, encompasses a spectrum of liver diseases that are associated with hepatic steatosis.[1] A recent multi-societal effort addressed the limitation of the terms "nonalcoholic fatty liver disease (NAFLD)" and "nonalcoholic steatohepatitis (NASH)" and decided on the terminology of "metabolic dysfunction-associated steatotic liver disease (MASLD)" and "metabolic dysfunction-associated steatohepatitis (MASH)".[2] Based on the diagnostic criteria for the two conditions which are similar but not identical, there is a significant overlap between NAFLD and MASLD as well as NASH and MASH.[2,3]

The decision to change the name was partly due to the assumption that the term NAFLD might be associated with stigma. People with NAFLD, especially those with obesity, may experience stigma not only for their weight but also for their associated comorbidities including the diagnosis of NAFLD.[4–9] In the past, concerns about NAFLD and NASH were focused on the terms "fat" and "alcoholic" which were considered potentially stigmatizing.[8] A recent global survey of providers and patients with NAFLD confirmed that stigma was consistently associated with overweight or obesity while the perception of stigma related to NAFLD as a disease or its specific diagnostic terms varied among regions of the world as well as between patients and providers.[9] In this context, <10% of patients reported having experienced stigmatization or discrimination due to the liver disease of NAFLD but that proportion was as high as 45% in some regions of the world.[9] In contrast, 38% and 34% of providers believed the terms "fatty" and "nonalcoholic" were stigmatizing.[9]

In the context of this discordance between patients' and providers' perception, the impact of stigma on patients' health-related quality of life (HRQL) is not well-known. The aims of this multicenter observational prospectively designed study were to assess the impact of experienced stigma on HRQL among patients with NAFLD and to identify domains of the disease burden which can potentially impact patients and their communication with providers.

Patients and methods

A survey targeting patients with NAFLD was developed by the members of the Global NASH Council (globalnashcouncil.org). At the time of the study design, the nomenclature change from NAFLD/NASH to MASLD/MASH had not yet been decided so the entire survey was worded around NAFLD and NASH. The members of Global NASH Council, after obtaining approval from their respective institutional review boards or other supervisory institutions, distributed links to the survey among their patients who had an established diagnosis of NAFLD or NASH; an electronic informed consent form was included with the surveys. Other than having NAFLD or NASH and willingness and ability to complete the survey, no inclusion/exclusion criteria were recommended by the study protocol.[9]

The patient survey included questions about individuals' basic demographics, select socio-economic parameters, presence/severity of liver fibrosis and non-hepatic comorbidities, experience with discrimination or stigmatization due to liver disease and other health conditions, and whether any of various diagnostic terms for NAFLD would make them feel comfortable or uncomfortable.[9]

The patient survey also included a specifically designed 35-item liver disease burden (LDB) questionnaire; the questionnaire was developed for this study with the aim to cover various aspects of the disease burden in the context of NAFLD and NASH (Table S1). To develop the questionnaire, the items were suggested by members of the Global NASH Council based on their expert opinion, review of the literature, and communication with patients, and then systematically reviewed by a panel of experts for relevance, readability, and comprehensiveness. Translations of the questionnaire to non-English languages were performed centrally using a professional medical translation service with forward/backward translation.

In all the items of LDB, participants were asked to what extent they agree with a certain statement regarding their disease burden (for example: "I feel uncomfortable because I am a person with liver disease"); the responses were scored 1-4 with higher scores indicating a greater self-reported disease burden. With the aim to yield interpretable domains of LDB, the items were subjected to exploratory factor analysis. The items were then grouped into domains based on the highest factor loadings, and the LDB domain scores were calculated as an average of their constituent items.

After completing the clinico-demographic part of the survey, the stigma and diagnostic terms-related questions followed by the LDB questionnaire, participants were offered (but not required) to complete the chronic liver disease questionnaire (CLDQ)-NASH, a validated disease-specific HRQL instrument for NAFLD and NASH, in the same language as the main survey using a validated translation of the instrument. The CLDQ-NASH instrument includes 36 items scored 1-7 (higher scores indicate better quality of life) grouped into six domains.[10]

Only participants who completed the survey up to the last question of LDB and clicked the "submit" button were included in the study. No other exclusion criteria were applied. The survey was administered electronically via a secure weblink without collection of any identifier. The completed survey data were stored in a central database.

Statistical analysis

All participants who completed LDB were included and grouped based on the region of the world in which they resided. The frequencies of answers were summarized as n (%) and compared between the groups using the chi-square test; the non-parametric Mann-Whitney test was used for continuous variables. Exploratory factor analysis was used to identify different domains of the LDB questionnaire, with the aim to explain 95% of variance in the data. For participants who completed both LDB and CLDQ-NASH, correlations between domains of the two instruments were assessed using non-parametric Spearman's coefficient. Independent predictors of CLDQ-NASH scores were evaluated using linear mixed-effects regression models which included age, sex, education, BMI, elements of medical history, the presence of type 2 diabetes, severe fibrosis, experience with stigma due to NAFLD or overweight/obesity, and negative perception of various diagnostic terms for NAFLD as fixed effects

and the country of residence as a random effect. Two-sided p values less than 0.05 were considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 2,117 patients from 24 countries completed the entire survey (Tables 1 and S2). Of the participants, 48% were from the Middle East and North Africa (MENA) region, 18% from Europe, 16% from USA/Canada, 14% from South-East (SE) Asia, and 4% from South Asia; 60% were males; 57% had a 4-year college degree; 65% were employed; 50% had at least one comorbidity, while 27% had two or more comorbidities; and 30% had a history of diabetes or high blood sugar. Of these study participants who completed the survey with LDB, 778 also completed the CLDQ-NASH (Table 1).

Liver disease burden

Out of 35 items of LDB (seven domains), the greatest burden scores were observed for the following items: "I feel like I am partially to blame for my liver disease" (mean score 2.17 on a 1-4 scale, a higher score indicates worse burden) and "Some people believe I have liver disease because I do not eat properly" (mean score 2.13) (Table 2). There was a substantial regional variability in LDB responses, with the highest average burden scores seen among patients from the USA and the lowest among those from MENA (Table 2, Fig. 1). Regarding their interaction with healthcare providers, 5.8% believed that "some doctors or nurses don't like taking care of patients with liver disease", with this proportion being as high as 18.4% in the USA.

After factor analysis of the 35 LDB items, we found that 95% of variance could be explained by seven factors. The LDB items were grouped based on their highest factor loadings into the domains which were subsequently named as follows: Social life, Stigma, Self-perception, Isolation, Term "fatty", Term "nonalcoholic", and Healthcare (Table S1).

Across LDB domains, the average scores were the highest for the Stigma domain (the only domain with the mean score greater than 2.0) and the lowest for Isolation and Social Life domains (i.e., the disease burden related to these aspects was the lowest). The average domain scores by the region of enrollment followed a similar pattern to that reported above for the individual items: for 3/7 domain scores and the total score, the highest average scores (indicating the greatest burden) were observed in patients with NAFLD from the USA, the lowest in patients from Europe and MENA. However, for the Stigma domain, the scores of patients from the USA and Europe were the highest while patients from the MENA region had the lowest scores (i.e., the lowest disease burden related to stigma) (Table 2, Fig. 2).

Health-related quality of life: CLDQ-NASH

Of the entire sample of patients with NAFLD, 9% reported having been stigmatized due to NAFLD at least sometimes (up to 22% in the USA) while 26% reported stigmatization due to overweight or obesity (57% in the USA) (Table S2). Furthermore, 16-21% reported being uncomfortable with select diagnostic terms for NAFLD (up to 47% in the USA) (Table S2).

To assess the impact of stigma on HRQL, we analyzed data from 778 patients with NAFLD who, in addition to LDB, also completed CLDQ-NASH (Table 1). The highest CLDQ-NASH scores

(best quality of life) were observed in participants from Europe and MENA, and the lowest in those from the USA and SE Asia; the latter was primarily driven by the lowest fatigue scores (the most profound fatigue) (Table 3). Correlations of CLDQ-NASH scores with LDB scores were all statistically significant of moderate magnitude, between -0.17 and -0.40 in magnitude (all p <0.0001) (Table S3).

Participants who reported experience with stigmatization due to liver disease (NAFLD) had significantly lower CLDQ-NASH scores in comparison to those who did not report history of stigma due to NAFLD (by up to -1.1 points, or 18% of the range size, for the Worry domain; all p <0.0001) (Tables 4 and S4). The association of stigmatization due to overweight/obesity with lower CLDQ-NASH scores was also significant (all p <0.0001) but the effect size was smaller (up to -0.57, or 10% of the range size, in the Fatigue domain) (Table 4).

In multivariate analysis adjusted for age, sex, BMI, country and area of residence, socio-economic parameters (education, home ownership, healthcare coverage, current financial situation), comorbidities, and fibrosis severity, we found that experience with stigmatization or discrimination due to the liver disease of NAFLD was the strongest independent predictor of lower CLDQ-NASH scores in all domains (beta from -0.29 to -0.48, all p <0.05) (Table 5). In addition, experience with stigmatization due to overweight/obesity was associated with lower Activity, Emotional Health, Fatigue, and Worry domain scores (beta from -0.20 to -0.30, p <0.05) (Table 5). Finally, being uncomfortable with the diagnostic term "fatty liver disease" was independently associated with lower Emotional Health scores (beta = -0.43, p = 0.0018) (Table 5). Other significant predictors of impairment in select CLDQ-NASH scores included female sex, having major financial problems, having ≥2 chronic comorbidities, history of weight loss due to medical reasons, and having severe fibrosis or cirrhosis (p <0.05) (Table S5).

Liver disease severity and disease burden
Since the presence of advanced liver disease can be associated with both stigma and quality of life, we sought to investigate its contribution in our sample. Out of 2,117 participants included in this study, 1,383 (65%) knew their stages of fibrosis, and of those, 12% reported having severe fibrosis and 6% cirrhosis. Participants who had severe fibrosis or cirrhosis were older, less educated or employed, with higher BMI, and had significantly more comorbidities (including type 2 diabetes) (Table S6). In addition, those

Table 1. Socio-demographic characteristics and medical history of patients with NAFLD who completed the LDB survey and CLDQ-NASH.

Description	Participants with HRQL, n (%)	Participants with LDB, n (%)
N	778	2,117
Age group		
18-24 years	15 (1.9%)	143 (6.8%)
25-34 years	49 (6.3%)	352 (16.6%)
35-44 years	134 (17.2%)	465 (22.0%)
45-54 years	164 (21.1%)	406 (19.2%)
55-70 years	331 (42.5%)	606 (28.6%)
>70 years	85 (10.9%)	145 (6.8%)
Male	393 (50.5%)	1,274 (60.2%)
Female	385 (49.5%)	843 (39.8%)
BMI, kg/m^2	31.8 ± 9.8	29.2 ± 8.6
Place of residence		
Urban area	294 (37.8%)	1,140 (54.0%)
Suburban area	344 (44.3%)	703 (33.3%)
Rural area	139 (17.9%)	269 (12.7%)
Education		
No schooling completed	46 (5.9%)	71 (3.4%)
Up to 6 years (primary school)	148 (19.0%)	262 (12.4%)
Up to 12 years (high school)	241 (31.0%)	573 (27.2%)
Bachelor's degree	251 (32.3%)	942 (44.7%)
Post-graduate degree	91 (11.7%)	261 (12.4%)
Lives with a partner	568 (73.1%)	1,455 (69.0%)
Employed	399 (51.6%)	1,376 (65.3%)
Owns a home	549 (70.7%)	1,250 (59.2%)
Current financial difficulties		
None	450 (58.0%)	1,415 (67.1%)
A little	240 (30.9%)	542 (25.7%)
A lot	86 (11.1%)	152 (7.2%)
Has healthcare coverage	641 (82.4%)	1,717 (81.3%)
Ever lost weight for medical reasons	317 (41.7%)	559 (26.8%)
Chronic illnesses or health problems in addition to NAFLD/NASH		
None	201 (26.0%)	1,053 (50.1%)
One	219 (28.3%)	475 (22.6%)
Two	171 (22.1%)	290 (13.8%)
Three or more	183 (23.6%)	285 (13.6%)
Diabetes or high blood sugar	301 (38.7%)	625 (29.7%)
Know their fibrosis severity	360 (46.3%)	1,366 (69.1%)
Minimal or moderate fibrosis	232 (64.4%)	1,133 (81.9%)
Severe fibrosis	76 (21.1%)	164 (11.9%)
Cirrhosis	52 (14.4%)	86 (6.2%)

The countries of enrollment are shown in Table S7.
HRQL, health-related quality of life; LDB, liver disease burden; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Table 2. LDB item scores on a scale of 1-4.

LDB item (LDB domain)	Europe Mean ± SD	MENA Mean ± SD	SE Asia Mean ± SD	South Asia Mean ± SD	USA Mean ± SD	p value*	All Mean ± SD
N	373	1,014	305	90	335		2,117
Identifying as person with liver disease is a burden for me (Self-perception)	2.11 ± 0.95	1.85 ± 0.67	2.05 ± 0.85	2.01 ± 0.51	1.97 ± 0.87	<0.0001	1.95 ± 0.78
Identifying as a person with liver disease causes me inconvenience in my daily life (Self-perception)	1.68 ± 0.78	1.86 ± 0.69	1.94 ± 0.79	2.11 ± 0.55	1.87 ± 0.82	<0.0001	1.85 ± 0.74
To be identified as a person with liver disease hurts my life (Self-perception)	1.60 ± 0.75	1.88 ± 0.72	2.00 ± 0.82	2.00 ± 0.48	1.87 ± 0.80	<0.0001	1.85 ± 0.75
I feel uncomfortable because I am a person with liver disease (Self-perception)	2.11 ± 0.90	1.95 ± 0.76	2.08 ± 0.87	2.04 ± 0.54	2.02 ± 0.88	0.0126	2.01 ± 0.82
I am afraid that others will know that I am a person with liver disease (Self-perception)	1.62 ± 0.74	1.69 ± 0.51	1.85 ± 0.76	1.88 ± 0.52	1.82 ± 0.81	<0.0001	1.73 ± 0.65
I feel like I can't do anything about my liver disease status (Self-perception)	2.10 ± 0.82	1.83 ± 0.69	1.85 ± 0.69	1.97 ± 0.51	2.11 ± 0.86	<0.0001	1.93 ± 0.75
I set myself apart from others because I am a person with liver disease (Isolation)	1.68 ± 0.73	1.69 ± 0.54	1.71 ± 0.64	1.89 ± 0.44	1.71 ± 0.71	0.0046	1.70 ± 0.62
I avoid interacting with others because I am a person with liver disease (Isolation)	1.38 ± 0.55	1.68 ± 0.51	1.65 ± 0.60	1.88 ± 0.42	1.56 ± 0.60	<0.0001	1.61 ± 0.56
I hesitate to make new friends in case they discover that I am a person with liver disease (Isolation)	1.36 ± 0.54	1.68 ± 0.53	1.65 ± 0.61	1.86 ± 0.44	1.50 ± 0.57	<0.0001	1.60 ± 0.56
Some people assume that because I have liver disease, I must have been a drinker (Stigma)	2.20 ± 1.01	1.70 ± 0.53	1.79 ± 0.73	1.89 ± 0.61	2.65 ± 0.94	<0.0001	1.96 ± 0.82
Other people think I am partially to blame for my liver disease (Stigma)	2.20 ± 0.92	1.79 ± 0.62	2.05 ± 0.81	1.96 ± 0.62	2.61 ± 0.96	<0.0001	2.03 ± 0.82
Some people believe I have liver disease because I do not eat properly (Stigma)	2.28 ± 0.91	1.90 ± 0.73	2.20 ± 0.82	2.14 ± 0.73	2.62 ± 0.93	<0.0001	2.13 ± 0.85
I feel like some people are concerned that my liver disease could be contagious (Social life)	1.42 ± 0.65	1.70 ± 0.53	1.78 ± 0.72	1.76 ± 0.50	1.53 ± 0.63	<0.0001	1.64 ± 0.61
I feel like other people think I am a bad person because I have liver disease (Social life)	1.48 ± 0.67	1.68 ± 0.49	1.62 ± 0.60	1.78 ± 0.49	1.80 ± 0.81	<0.0001	1.66 ± 0.60
People with liver disease are looked down upon by society (Stigma)	1.89 ± 0.81	1.68 ± 0.50	1.62 ± 0.62	1.78 ± 0.51	2.19 ± 0.90	<0.0001	1.79 ± 0.68
Because I have NAFLD or NASH, some people assume I must be overweight or have been in the past (Stigma)	2.36 ± 0.97	1.78 ± 0.62	2.23 ± 0.82	2.22 ± 0.70	2.64 ± 0.91	<0.0001	2.10 ± 0.84
Some doctors or nurses don't like taking care of patients with liver disease (Healthcare)	1.50 ± 0.64	1.68 ± 0.51	1.66 ± 0.60	1.79 ± 0.51	1.87 ± 0.80	<0.0001	1.68 ± 0.61
I feel I have been treated with less respect by others because of my liver disease (Social life)	1.48 ± 0.66	1.68 ± 0.51	1.65 ± 0.58	1.76 ± 0.50	1.84 ± 0.79	<0.0001	1.67 ± 0.61
I believe when people learn I have liver disease they treat me differently than if I did not have this disease (Social life)	1.59 ± 0.71	1.72 ± 0.57	1.74 ± 0.67	1.83 ± 0.50	1.94 ± 0.83	<0.0001	1.74 ± 0.66
When diagnosed with NAFLD or NASH, I felt shame when hearing the words "nonalcoholic." (Term "alcoholic")	1.67 ± 0.70	1.71 ± 0.57	1.76 ± 0.66	1.81 ± 0.54	1.77 ± 0.79	0.08	1.73 ± 0.64
When diagnosed with NAFLD or NASH, I felt shame when hearing the word "fatty." (Term "fatty")	1.98 ± 0.83	1.71 ± 0.54	1.85 ± 0.68	1.86 ± 0.57	2.40 ± 0.94	<0.0001	1.89 ± 0.73
I feel like I am partially to blame for my liver disease (Stigma)	2.28 ± 0.78	1.86 ± 0.68	2.40 ± 0.85	1.87 ± 0.58	2.83 ± 0.88	<0.0001	2.17 ± 0.84
I feel less competent that I did before I was diagnosed with liver disease (Social life)	1.62 ± 0.75	1.80 ± 0.62	1.92 ± 0.72	1.91 ± 0.57	1.95 ± 0.84	<0.0001	1.82 ± 0.70
Because of my liver disease, I feel flawed and incomplete (Stigma)	1.78 ± 0.81	1.72 ± 0.54	1.87 ± 0.73	1.86 ± 0.57	2.10 ± 0.91	<0.0001	1.81 ± 0.70
Because of my liver disease, I sometimes feel useless (Social life)	1.50 ± 0.64	1.70 ± 0.52	1.70 ± 0.62	1.92 ± 0.43	1.80 ± 0.80	<0.0001	1.69 ± 0.61
I avoid telling other people about my liver disease (Stigma)	2.43 ± 0.83	1.72 ± 0.54	1.86 ± 0.70	1.90 ± 0.48	2.38 ± 0.92	<0.0001	1.98 ± 0.76
I feel lonely more often than usual because of my liver disease (Social life)	1.47 ± 0.64	1.70 ± 0.53	1.85 ± 0.72	1.83 ± 0.46	1.70 ± 0.72	<0.0001	1.69 ± 0.61
I feel like I am an outsider because of my liver disease (Social life)	1.40 ± 0.55	1.67 ± 0.49	1.71 ± 0.57	1.84 ± 0.47	1.70 ± 0.72	<0.0001	1.64 ± 0.57
I avoid doing some things in public because of my liver disease (Social life)	1.48 ± 0.67	1.67 ± 0.49	1.72 ± 0.62	1.90 ± 0.45	1.69 ± 0.74	<0.0001	1.66 ± 0.59
My liver disease makes me stand out to other people (Social life)	1.54 ± 0.71	1.70 ± 0.53	1.67 ± 0.58	1.80 ± 0.43	1.63 ± 0.68	<0.0001	1.66 ± 0.60
Some people avoid me because of my liver disease (Social life)	1.38 ± 0.53	1.67 ± 0.49	1.68 ± 0.59	1.84 ± 0.47	1.55 ± 0.62	<0.0001	1.61 ± 0.54
I feel abandoned by family members because of my liver disease (Social life)	1.33 ± 0.51	1.64 ± 0.48	1.56 ± 0.52	1.78 ± 0.49	1.50 ± 0.59	<0.0001	1.56 ± 0.53
Since my diagnosis of NAFLD or NASH I feel less socially involved and engaged (Social life)	1.44 ± 0.63	1.70 ± 0.53	1.68 ± 0.58	1.87 ± 0.53	1.79 ± 0.82	<0.0001	1.67 ± 0.62
Does it bother you that your liver problem is called nonalcoholic? (Term "alcoholic")	1.62 ± 0.72	1.72 ± 0.58	1.84 ± 0.67	1.84 ± 0.50	1.76 ± 0.80	<0.0001	1.73 ± 0.66
Does it bother you that your liver problem is called fatty liver? (Term "fatty")	1.76 ± 0.78	1.73 ± 0.56	2.03 ± 0.76	1.92 ± 0.46	2.28 ± 0.98	<0.0001	1.87 ± 0.74
LDB domain scores:							
Social life	1.47 ± 0.53	1.69 ± 0.48	1.71 ± 0.49	1.83 ± 0.39	1.72 ± 0.59	<0.0001	1.67 ± 0.51
Stigma	2.18 ± 0.58	1.77 ± 0.51	2.00 ± 0.52	1.95 ± 0.44	**2.50 ± 0.71**	<0.0001	2.00 ± 0.62
Self-perception	1.87 ± 0.64	1.84 ± 0.59	1.96 ± 0.63	2.00 ± 0.37	1.95 ± 0.66	0.0013	1.89 ± 0.61
Isolation	1.47 ± 0.53	1.68 ± 0.50	1.67 ± 0.57	1.87 ± 0.33	1.59 ± 0.56	<0.0001	1.64 ± 0.53
Term "fatty"	1.87 ± 0.74	1.72 ± 0.52	1.94 ± 0.63	1.88 ± 0.47	**2.33 ± 0.92**	<0.0001	1.88 ± 0.69
Term "alcoholic"	1.65 ± 0.64	1.72 ± 0.56	1.80 ± 0.56	1.83 ± 0.46	1.76 ± 0.72	0.0004	1.73 ± 0.60
Healthcare burden	1.50 ± 0.64	1.68 ± 0.51	1.66 ± 0.60	1.79 ± 0.51	**1.87 ± 0.80**	<0.0001	1.68 ± 0.61
Total score	1.74 ± 0.49	1.74 ± 0.48	1.84 ± 0.47	1.89 ± 0.33	**1.97 ± 0.56**	<0.0001	1.79 ± 0.50

Strongly disagree = 1; Disagree = 2; Agree = 3; Strongly agree = 4; higher score indicates worse burden; mean ± SD.
LDB, liver disease burden; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
* p value returned by Mann-Whitney non-parametric test.
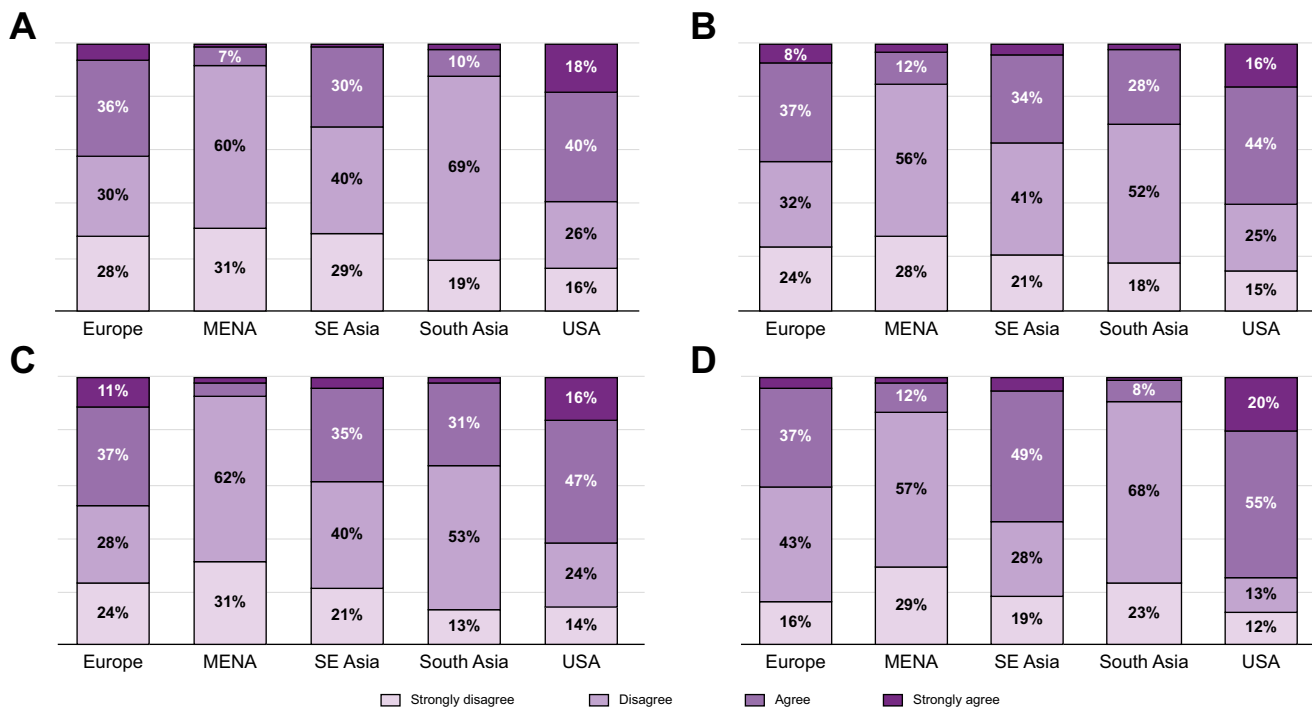
Fig. 1. The items of LDB which returned the highest average burden scores among patients with NAFLD, by the region of enrollment. (A) Other people think I am partially to blame for my liver disease; (B) Some people believe I have liver disease because I do not eat properly; (C) Because I have NAFLD or NASH, some people assume I must be overweight or have been in the past; (D) I feel like I am partially to blame for my liver disease. LDB, liver disease burden; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
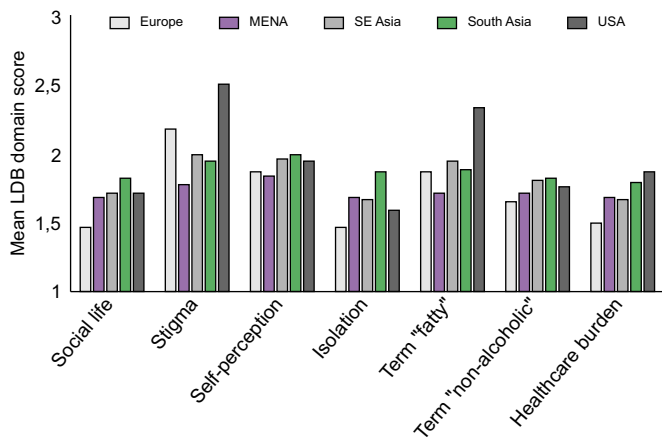
Fig. 2. Average LDB scores (range 1-4, higher score indicates greater burden) of patients with NAFLD by the region of residence. LDB, liver disease burden; NAFLD, nonalcoholic fatty liver disease.

with advanced liver disease reported more stigma (25% *vs.* 6% due to NAFLD, 42% *vs.* 18% due to obesity), greater disease burden in all LDB domains (the greatest burden in the Stigma domain) and, of those who also had HRQL data (n = 360), had decreased scores in all domains of CLDQ-NASH: total score 5.12 ± 1.01 *vs.* 5.51 ± 1.09, all *p* <0.05 (Table S6). In multivariate analysis, independent association of advanced liver disease with CLDQ-NASH scores was still significant for the Worry domain (beta = -0.47 ± 0.12, *p* = 0.0001) (Table S5).

Discussion

This is a large global study assessing perceived liver disease burden among patients with NAFLD (recently renamed MASLD) and the association of stigma, a global research priority,[11] with HRQL scores. In this study, we have shown that the disease burden associated with NAFLD/MASLD is multifactorial but the greatest burden, as manifested via the highest LDB scores, is indeed associated with the stigma related to NAFLD. However, in the context of liver disease burden, there are substantial regional differences so that the highest disease burden scores across multiple domains were observed in the USA, where the prevalence of obesity is higher and associated social deprivation may exacerbate this burden.[7] At the same time, patients from Europe reported relatively low overall disease burden as manifested by the lowest burden scores in most domains, with the only exception being the domain of stigma. In contrast, patients from MENA reported the lowest disease burden and, in particular, the least stigma related to both NAFLD and overweight/obese. This reduced stigma perception may be attributable to the presence of strong cultural factors, including the cultural appreciation of plumpness – especially in women – regarded more as a positive connotation of prosperity, fertility and good health than a sign of health risk.[12]

In the context of the perceived liver disease burden, it may be illustrative to put it in the context of providers' perception. In our prior study, we have shown that more than 88% of providers believed that overeating and sedentary lifestyle were among the causes of NAFLD, up to 46% felt uncomfortable taking care of patients with NAFLD because they felt those patients lacked the willpower, motivation or self-control necessary for lifestyle

Table 3. The CLDQ-NASH scores of patients with NAFLD by the region of residence. The scores range 1-7, greater scores represent better HRQL.

CLDQ-NASH score (range 1-7; mean ± SD)	Europe n = 277	MENA n = 114	SE Asia n = 200	USA n = 187	*p* value*	All N = 778
Abdominal symptoms	5.61 ± 1.43	5.32 ± 1.66	4.87 ± 1.59	5.16 ± 1.54	<0.0001	5.27 ± 1.56
Activity and energy	5.78 ± 1.10	5.25 ± 1.56	4.78 ± 1.35	5.41 ± 1.35	<0.0001	5.35 ± 1.36
Emotional well-being	5.77 ± 1.05	5.23 ± 1.65	4.69 ± 1.37	5.08 ± 1.23	<0.0001	5.25 ± 1.35
Fatigue	5.34 ± 1.23	4.73 ± 1.80	4.32 ± 1.27	4.30 ± 1.41	<0.0001	4.74 ± 1.46
Systemic symptoms	5.77 ± 0.93	5.02 ± 1.62	4.79 ± 1.31	5.07 ± 1.15	<0.0001	5.24 ± 1.27
Worry	6.11 ± 0.93	6.01 ± 1.18	4.73 ± 1.54	5.33 ± 1.43	<0.0001	5.55 ± 1.39
Total score	5.73 ± 0.81	5.26 ± 1.31	4.70 ± 1.21	5.06 ± 1.08	<0.0001	5.23 ± 1.14

HRQL, health-related quality of life; LDB, liver disease burden; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
* *p* value returned by Mann-Whitney non-parametric test.

Table 4. CLDQ-NASH scores of patients with NAFLD by the presence of experience with stigmatization (at least sometimes *vs.* rarely or never).

CLDQ-NASH score (range 1-7)	Experience with stigma or discrimination	No experience with stigma or discrimination	*p* value*
Due to liver disease (NAFLD)			
Abdominal symptoms	4.47 ± 1.67	5.38 ± 1.51	<0.0001
Activity and energy	4.64 ± 1.36	5.46 ± 1.33	<0.0001
Emotional well-being	4.42 ± 1.36	5.37 ± 1.30	<0.0001
Fatigue	3.89 ± 1.36	4.86 ± 1.43	<0.0001
Systemic symptoms	4.57 ± 1.30	5.33 ± 1.24	<0.0001
Worry	4.59 ± 1.54	5.69 ± 1.31	<0.0001
Total score	4.43 ± 1.14	5.35 ± 1.10	<0.0001
Due to overweight/obesity			
Abdominal symptoms	5.02 ± 1.62	5.42 ± 1.50	0.0005
Activity and energy	5.07 ± 1.39	5.52 ± 1.31	<0.0001
Emotional well-being	4.94 ± 1.36	5.43 ± 1.31	<0.0001
Fatigue	4.38 ± 1.43	4.95 ± 1.43	<0.0001
Systemic symptoms	5.01 ± 1.24	5.37 ± 1.27	<0.0001
Worry	5.25 ± 1.44	5.73 ± 1.33	<0.0001
Total score	4.94 ± 1.14	5.41 ± 1.11	<0.0001

Demographic and clinical parameters of the two patient groups are described in Table S4.
NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
* *p* value returned by Mann-Whitney non-parametric test.

changes, and 45% felt that patients with NAFLD did not take care of their diabetes.[9] Also, while only 8% providers reported difficulty feeling empathy for their patients with NAFLD or having negative reactions towards their appearance, 33% said that treating patients with NAFLD and NASH was frustrating for them.[9] At the same time, in this study, the LDB item of healthcare that described the relationship with providers from patients' perspective had a relatively low burden score (mean 1.68 in a 1-4 scale); indeed, less than 6% patients believed that providers might not like to care for patients with NAFLD like themselves. On the other hand, one of the most severe disease burden aspects was related to self-blame so that up to 33% patients believed that they were at least partially to blame for their liver disease or that others might think as much about them. This suggests that although patients do not commonly believe or directly experience the negative attitude of providers towards them, providers being a part of the general society may still contribute to the attitude that results in patients' guilt and self-blame, which likely adds to the disease burden.

As previously reported, less than 10% of patients report having experienced stigma or discrimination due to NAFLD (although that proportion was higher in some regions).[9] In this analysis, we show that despite being infrequent, patients who report stigma due to NAFLD have significantly worse HRQL scores in all domains of CLDQ-NASH. Furthermore, that association remained strong even after adjustment for other HRQL

predictors which makes experience with stigmatization due to NAFLD a major predictor of HRQL impairment in this patient population. While a much greater proportion of patients with NAFLD reported discrimination or stigma due to obesity, a similar negative association was observed in fewer domains of CLDQ-NASH and had a smaller effect size after adjustment for confounders. The association of stigmatization with HRQL impairment in NAFLD, especially in the presence of advanced liver disease, has previously been reported in single-center studies from Spain, Denmark, and a safety-net clinic from California.[6,13,14] Our findings strengthen the growing evidence that addressing stigma in NAFLD/MASLD could be essential for improving patients' well-being and self-efficacy with this condition for which successful treatment must include lifestyle interventions.[15,16]

Similar findings indicating a strong association between stigma and obesity have previously been documented, including among patients with NAFLD.[17–19] In the current study, we have shown that being uncomfortable with the diagnostic term "fatty liver disease" was more frequently reported by people with lower Emotional Health scores which may be a proxy of impaired mental health. Altogether, these observed associations suggest that while the burden of stigma associated with NAFLD may not be overwhelming in comparison to stigma associated with obesity, when present, it manifests as a major predictor of a substantial impairment in quality of life.

Table 5. Independent association of CLDQ-NASH scores with having experienced stigma/discrimination due to NAFLD and overweight/obesity and with perception of various diagnostic terms for NAFLD.

CLDQ-NASH domain score	Predictor	Beta (95% CI)	*p* value
Abdominal symptoms	Stigmatized or discriminated due to liver disease (NAFLD)	-0.41 (-0.75 to -0.06)	0.0210
	Stigmatized or discriminated due to being overweight/obesity	-0.14 (-0.38 to 0.10)	0.26
	Uncomfortable with "fatty liver disease"	-0.35 (-0.68 to -0.02)	0.0396
	Uncomfortable with "NAFLD"	0.36 (0.01 to 0.71)	0.0415
	Uncomfortable with "MAFLD"	-0.09 (-0.43 to 0.24)	0.59
Activity and energy	Stigmatized or discriminated due to liver disease (NAFLD)	-0.33 (-0.61 to -0.06)	0.0189
	Stigmatized or discriminated due to being overweight/obesity	-0.30 (-0.49 to -0.10)	0.0026
	Uncomfortable with "fatty liver disease"	-0.20 (-0.47 to 0.07)	0.15
	Uncomfortable with "NAFLD"	0.16 (-0.12 to 0.44)	0.27
	Uncomfortable with "MAFLD"	-0.14 (-0.40 to 0.13)	0.32
Emotional well-being	Stigmatized or discriminated due to liver disease (NAFLD)	-0.48 (-0.75 to -0.20)	0.0007
	Stigmatized or discriminated due to being overweight/obesity	-0.22 (-0.41 to -0.03)	0.0247
	Uncomfortable with "fatty liver disease"	-0.43 (-0.70 to -0.16)	0.0018
	Uncomfortable with "NAFLD"	0.15 (-0.12 to 0.42)	0.28
	Uncomfortable with "MAFLD"	-0.12 (-0.39 to 0.14)	0.36
Fatigue	Stigmatized or discriminated due to liver disease (NAFLD)	-0.40 (-0.70 to -0.10)	0.0102
	Stigmatized or discriminated due to being overweight/obesity	-0.24 (-0.45 to -0.02)	0.0320
	Uncomfortable with "fatty liver disease"	-0.17 (-0.48 to 0.13)	0.26
	Uncomfortable with "NAFLD"	0.10 (-0.21 to 0.40)	0.54
	Uncomfortable with "MAFLD"	-0.08 (-0.37 to 0.21)	0.59
Systemic symptoms	Stigmatized or discriminated due to liver disease (NAFLD)	-0.29 (-0.54 to -0.04)	0.0212
	Stigmatized or discriminated due to being overweight/obesity	-0.14 (-0.31 to 0.03)	0.11
	Uncomfortable with "fatty liver disease"	-0.13 (-0.38 to 0.11)	0.28
	Uncomfortable with "NAFLD"	0.10 (-0.15 to 0.35)	0.43
	Uncomfortable with "MAFLD"	-0.09 (-0.33 to 0.15)	0.48
Worry	Stigmatized or discriminated due to liver disease (NAFLD)	-0.38 (-0.65 to -0.11)	0.0061
	Stigmatized or discriminated due to being overweight/obesity	-0.20 (-0.39 to -0.01)	0.0385
	Uncomfortable with "fatty liver disease"	-0.30 (-0.57 to -0.03)	0.0325
	Uncomfortable with "NAFLD"	0.01 (-0.26 to 0.29)	0.92
	Uncomfortable with "MAFLD"	-0.30 (-0.56 to -0.04)	0.0263
Total score	Stigmatized or discriminated due to liver disease (NAFLD)	-0.39 (-0.60 to -0.17)	0.0005
	Stigmatized or discriminated due to being overweight/obesity	-0.20 (-0.35 to -0.05)	0.0099
	Uncomfortable with "fatty liver disease"	-0.26 (-0.48 to -0.05)	0.0168
	Uncomfortable with "NAFLD"	0.15 (-0.07 to 0.36)	0.18
	Uncomfortable with "MAFLD"	-0.13 (-0.34 to 0.08)	0.22

Associations adjusted for age, sex, education, BMI, comorbidities, and fibrosis severity as fixed effects, country of residence as a random effect.
MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

In the context of the recent nomenclature change, our data collected with the LDB instrument may shed some light onto patients' perception. Only 8% of our patients agreed that it bothered them that the disease had the word "nonalcoholic" in its name (up to 16% in the USA). Regarding the term "fatty", the pooled proportion of those bothered or ashamed by it was 16% but 50% in the USA. Given this, the change from "fatty" to "metabolic" in the name of the condition may be justified while the use of "nonalcoholic" did not seem to have substantially contributed to patients' discomfort.

The strength of this study is that it is multicenter, multinational and included patients from most regions of the world, helping to make the findings more generalizable globally; however, there was some imbalance in the regional representation. Furthermore, due to the design of the study, only a subsample of participants originally enrolled to the parent study with the LDB chose to complete the HRQL questionnaire. Since completion of the HRQL questionnaire was optional, it was prone to the non-response bias so that those from some sites, of poorer socio-economic status, with cirrhosis and other comorbidities were over-represented among HRQL completers. The lack of detailed clinical data limited the number of hypotheses available

to test and did not allow adjustment for potential confounders in the analysis of HRQL scores. The cross-sectional nature of the study does not allow one to interpret the associations found as causal. The entire sample of patients with NAFLD was likely biased towards patients of higher socio-economic status living in more developed regions (as confirmed by the rates of college education, home ownership, and financial difficulties in this sample) while patients who do not have a connection to a site led by a research physician affiliated with the Global NASH Council (which is the majority of patients with NAFLD worldwide who are typically seen by community-based primary care providers) remained beyond our survey outreach.

In conclusion, patients with NAFLD/MASLD and NASH/MASH report a substantial liver disease burden which is largely related to stigma and self-blame for their liver disease and/or associated conditions (including control of weight and diabetes), and to others blaming (or perceived as blaming) them for those disorders. In addition, while stigma related to NAFLD is not very common among patients, when patients feel stigmatized due to their NAFLD or obesity, this is strongly linked to a substantial impairment of their HRQL. Observed self-blame and discordance of attitude between patients and providers related to NAFLD/

MASLD burden and stigma may provide an opportunity to improve patient-provider communication. In this context, it is possible that interventions to address stigma may improve the HRQL and reduce disease burden in patients with NAFLD/ MASLD. The impact of the recent nomenclature changes to MASLD and MASH on patients' perception of stigma, HRQL and the overall liver disease burden should be assessed in future studies.

Abbreviations

CLDQ, chronic liver disease questionnaire; HRQL, health-related quality of life; LDB, liver disease burden; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MENA, Middle East and North Africa; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SE, South-East.

Conflict of interest

ZMY: research funding or consultation fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cymabay, GlaxoSmithKline, Intercept, Novo Nordisk, Siemens, Madrigal, Merck; YY: consulting/advisory board for Novo Nordisk, Cymabay, and Zydus. VWSW: served as a consultant or advisory board member for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, Visirna, speaker for Abbott, AbbVie, Gilead Sciences, Novo Nordisk, Unilab, received a research grant from Gilead Sciences, co-founder of Illuminatio Medical Technology Limited; AMA: grant funding from NIH, Novo Nordisk, Target Pharma, consulting/ advisory board for Novo Nordisk. JMS: consultant for Astra Zeneca, Apollo Endosurgery, Bayer, Boehringer Ingelheim, BMS, Gilead Sciences, GSK, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineers, receives research funding from Gilead Sciences, Boehringer Ingelheim, Siemens Healthcare GmbH, has stock options of AGED diagnostics, Hepta Bio, received speaker honorarium from Boehringer Ingelheim, Echosens, MedPublico GmbH, Novo Nordisk, Madrigal Pharmaceuticals, Histoindex, MedPublico GmbH.

CWS: speaker bureau fees from Gilead Sciences, Abbott; RL: receives funding support from NCATS, NIDDK, NHLBI, serves as a consultant to Aardvark Therapeutics, Altimmune, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Eli Lilly, Gilead, Glympse bio, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Takeda, Terns Pharmaceuticals and Viking Therapeutics. In addition, his institution received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sonic Incytes, Terns Pharmaceuticals, co-founder of LipoNexus Inc. PC: received research grants by MSD and Intercept. JVL reports grants from AbbVie, MSD, Gilead Sciences and Roche Diagnostics to his institution and speaker fees from Echosens, Gilead Sciences, and Novo Nordisk. SF: holds a senior clinical investigator fellowship from the Research Foundation Flanders (FWO) (1802154N). His institution has received grants from Astellas, Falk Pharma, Genfit, Gilead Sciences, GlympsBio, Janssens Pharmaceutica, Inventiva, Merck Sharp & Dome, Pfizer, Roche. He has acted as consultant for Abbvie, Actelion, Aelin Therapeutics, AgomAb, Aligos Therapeutics, Allergan, Alnylam, Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristoll-Meyers Squibb, CSL Behring, Coherus, Echosens, Dr. Falk Pharma, Eisai, Enyo, Galapagos, Galmed, Genetech, Genfit, Genflow Biosciences, Gilead Sciences, Intercept, Inventiva, Janssens Pharmaceutica, PRO.MED.CS Praha, Julius Clinical, Madrigal, Medimmune, Merck Sharp & Dome, Mursla Bio, NGM Bio, Novartis, Novo Nordisk, Promethera, Roche, Siemens Healthineers. SF has been lecturer for Abbvie, Allergan, Bayer, Eisai, Genfit, Gilead Sciences, Janssens Cilag, Intercept, Inventiva, Merck Sharp & Dome, Novo Nordisk,

Promethera, Siemens. AKS: Reports personal fees from Medscape Gastroenterology, Chronic Liver Disease Foundation, Medical Speakers Network, Up-to-Date; non-financial support from American Association for Study of Liver Diseases (AASLD), American College of Gastroenterology, and American Porphyria Foundation; grants from American College of Gastroenterology and National Institute of Health (NIAAA and NIDDK). Dr. Singal is a consultant on the SBIR grant for Pleiogenix pharmaceuticals and is DSMB member for phase 2-b trial of DUR-928 in alcoholic hepatitis for Durect Pharmaceuticals. In addition, apart from a steering committee member of the portal hypertension SIG and chair of the alcohol-associated liver disease SIG (2020-2022) of the AASLD, Dr. Singal currently is vice chair of the liver and biliary section of the AGA Council. None of these disclosures conflict with this activity.

LC reports lecture fees from Echosens, Gilead, Inventiva and Novo Nordisk, consultancy fees from Echosens, Novo Nordisk, Madrigal, MSD, Pfizer, Sagimet, and Siemens. NA: Grant/research support from 89Bio, AbbVie/Allergan, Akero, Better Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Corcept, DSM, Galectin, Genentech, Genfit, Gilead, Hepagene, Healio, Intercept, Inventiva, Ionis, Madrigal, Merck, NGM, Noom, NorthSea, Novo Nordisk, Perspectum, Pfizer, Poxel, Viking, and Zydus; speaker's fees from AbbVie/Allergan, Alexion, Echosens, Eisai, Exelixis, Gilead, Intercept, Perspectum, Salix, and Theratechnologies; Consultant for AbbVie/Allergan, Echosens, Fibronostics, Gilead, Intercept, Madrigal, Novo Nordisk, Perspectum, Pfizer, and Zydus. MEK: investigator/speaker/advisory board member: AstraZeneca, Roche, MSD, AbbVie, Eva, Mash Premier, Takeda, Organon, AUG, Inspire, HSO, Gilead, Janssen, Intercept, Rameda, Ipsen, Onxeo, MinaPharm, Pharco, Zeta, Alfa Cure, Bayer, Oncoustics, PDC, and Spimaco. JMS: Consultant - Astra Zeneca, Apollo Endosurgery, Bayer, Boehringer Ingelheim, Gilead Sciences, GSK, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineers. Research Funding: Gilead Sciences, Boehringer Ingelheim, Siemens Healthcare GmbH. Stock Options: AGED diagnostics, Hepta Bio. Speaker Honorarium: Boehringer Ingelheim, Echosens, Med-Publico GmbH, Novo Nordisk, Madrigal Pharmaceuticals, Histoindex, MedPublico GmbH. MK: Research grants: Madrigal + consulting and speaking, Akero, Cymabay, Inventiva, Intercept + consulting and speaking.Gilead + consulting and speaking, Viking, Bio89, Ipsen + consulting, Genfit, Bausch + consulting, Ionis, North Sea,Celgene,Genentech, High Tide, Tobira-Allergan, Abbvie + consulting and speaking, NOT research. MLY: Research support (grant) from Abbvie, BMS, Gilead, Merck and Roche diagnostics; Consultant of Abbvie, BMS, Gilead, Roche and Roche diagnostics; Speaker of Abbvie, BMS, Eisai, Gilead, Roche and Roche diagnostics. S.Z-S has given a onetime presentation for and received support for attending meetings and/or travel from AbbVie, and a onetime consultation for Siemens, outside of the submitted work.

PNN discloses the following financial relationship(s) on behalf of the University of Birmingham with a commercial interest: Grant/research support from Boehringer Ingelheim and Novo Nordisk; Consulting fees from Astra Zeneca, Boehringer Ingelheim, BMS, Gilead, GSK, Intercept, Madrigal, Novo Nordisk, Pfizer, Poxel Pharmaceuticals and Sun Pharma. Other coauthors report no conflicts of interest related to this study.

Please refer to the accompanying ICMJE disclosure forms for further details.

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manuscript; critical revision of the manuscript for important intellectual content; administrative, technical, or material support; study supervision. **C. Wendy Spearman:** acquisition of data; interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding; administrative, technical, or material support; study supervision. **Stuart K. Roberts:** acquisition of data; interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding; administrative, technical, or material support; study supervision. **Wah-Kheong Chan:** acquisition of data; interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding; administrative, technical, or material support; study supervision. **Marcelo Silva:** acquisition of data; interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding; administrative, technical, or material support; study supervision. **Andrei Racila:** database administration; critical revision of the manuscript for important intellectual content. **Pegah Golabi:** critical revision of the manuscript for important intellectual content. **Prooksa Ananchuensook:** acquisition of data; interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding; administrative, technical, or material support; study supervision. **Linda Henry:** study concept and design; data interpretation, drafting of the manuscript; critical revision of the manuscript for important intellectual content. **Maria Stepanova:** statistical analysis; interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. **Patrizia Carrieri:** study concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content. **Jeffrey V. Lazarus**: study concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Data availability statement

Data can be requested from the corresponding author.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101066.

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