

EXPLORING THE PATIENT PERCEIVED IMPACT OF NON-ALCOHOLIC STEATOHEPATITIS

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INTRODUCTION

- Nonalcoholic steatohepatitis (NASH) is a progressive form of nonalcoholic fatty liver disease (NAFLD), and is characterized by excessive liver fat accumulation, inflammation, liver cell injury and fibrosis¹
- The global prevalence of NAFLD is estimated at 24%; although NASH represents only 10-20% of NAFLD cases, it can potentially progress to advanced liver disease, leading to cirrhosis, liver-related mortality and hepatocellular carcinoma² and no treatment is currently approved
- Liver biopsy is currently the gold standard for confirmatory diagnosing of NASH, assessing the presence and extent of fibrosis and specific histological changes³
- NASH is associated with several comorbidities such as obesity, diabetes and cardiovascular diseases⁴
- NASH is often asymptomatic in early stages, but with progression patients may experience fatigue, impact on activity and emotional well-being⁵
- Data regarding the humanistic burden of NASH are scarce; thus, there is a need to understand the impact of NASH from patients' perspective

AIM

- The study aimed to explore the impact of NASH from the patients' perspective and to determine the availability of a suitable patient-reported outcomes (PRO) measure (PROM) for use in adults with confirmed NASH. Additionally the study aimed to develop a conceptual model for NASH

METHOD

Review of published literature

- A targeted literature review was conducted using MEDLINE® and Embase® (1996 – 2016) to identify:
 - the humanistic burden of disease in adult patients with diagnosed NASH and confirmed fibrosis, and
 - validated PROMs developed specifically for this patient population

Review of Grey Literature and Patient-Reported Qualitative Information

- A manual search of grey literature and congresses websites was conducted
- Patients blogs and patients groups websites including British Liver Trust⁶ and Global Liver Institute⁷ were also searched for qualitative information on the patients' experiences of living with NASH

Development of a Conceptual Model for NASH

- Areas of humanistic burden identified by the published and grey literature searches were summarized and reviewed by US and UK clinical experts and patient-advocacy representatives
- The results were used to develop an initial conceptual model for NASH which was used to determine the suitability of existing PROMs for this disease

RESULTS

- Few of the published studies assessed health-related quality of life (HRQoL) of a biopsy-confirmed NASH population only
- Studies presented burden of NAFLD across the spectrum of severity with NASH sometimes reported as a subgroup
 - The terms NASH and NAFLD were not always clearly differentiated

RESULTS (CONTD.)

PRO Instruments used in NASH

- No published data were found on a NASH-specific PROM, developed using FDA guidance for the specific patient population
- Table 1 presents the PROMs used in NASH/NAFLD patients available from the published literature

Table 1. PRO Instruments used in studies involving NASH patients

Generic PRO Instruments	Description
Short Form-36 (SF-36)⁸	<ul style="list-style-type: none"> A 36-item PRO instrument including eight HRQoL domains. Domain scores and two, additional summary scores are derived: Physical Component Summary (PCS) & Mental Component Summary Scores (MCS) All scores range from 0-100 with higher score indicating better HRQoL. Normative values available for US general population (mean of 50 and standard deviation [SD] 10)
Fatigue Impact Scale (FIS)⁹	<ul style="list-style-type: none"> A 40-item generic instrument composed of 3 subscales that describe how fatigue impacts cognitive, physical and psychosocial functioning Each item can be scored from 0 (no problem) to 4 (extreme problem); total score ranges from 0-160 Higher score reflects increasing fatigue impact
Patient Health Questionnaire (PHQ)¹⁰	<ul style="list-style-type: none"> Diagnostic instrument used in non-psychiatric setting to screen, diagnose, monitor and measure depression
Liver Disease Specific PRO Instruments	
Chronic Liver Disease Questionnaire (CLDQ)^{11,13}	<ul style="list-style-type: none"> A 29-item instrument developed to assess the impact of chronic liver conditions Comprises 6 domains: abdominal symptoms, activity, emotional, fatigue, systemic symptoms, and worry Scores range from 1 to 7 for all domains, with lower score indicating worse HRQoL Used with NAFLD patients¹² and recently its validity was measured in NASH patients¹³
CLDQ-NAFLD¹⁴	<ul style="list-style-type: none"> Comprises the 29-item CLDQ plus 7 additional NAFLD-specific items The content validity of the CLDQ-NAFLD for NASH patients has not yet been demonstrated Evaluation of the instrument in a group of NAFLD patients (including 50% with histological NASH) provides preliminary evidence of construct validity Responsiveness has yet to be evaluated in clinical trials involving NASH patients

HRQoL in NASH: Review of PROM Data

SF-36

- Patients with NAFLD/NASH had lower HRQoL than the US general population^{13,15} and the presence of advanced liver stages additionally decreased HRQoL¹⁵
- Compared with NAFLD patients without NASH, biopsy-confirmed NASH patients reported significantly worse PCS (Figure 1)¹⁶ as well as significantly worse vitality, bodily pain and general health scores (Figure 2)¹⁶
- Degree of fibrosis was reported to be associated with poorer HRQoL¹⁶

Figure 1. Comparison of SF-36 Summary Component Scores in patients with NASH vs NAFLD patients without NASH¹⁶

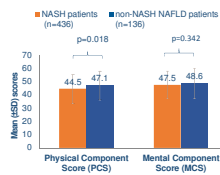
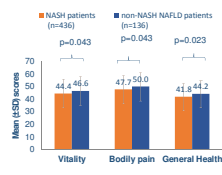


Figure 2. Comparison of SF-36 Domain Scores in patients with NASH vs NAFLD patients without NASH¹⁶



Fatigue

- Based on the Fatigue Impact Scale, NAFLD patients experienced significantly higher fatigue than matched non-NAFLD controls¹⁷
 - This study reported that fatigue does not seem to be associated with severity of liver fibrosis¹⁷

Psychological Impact

- Biopsy-confirmed NASH patients reported significantly increased lifetime rates of major depression disorder (odds Ratio, OR 3.8; 95% Confidence Interval, [CI], 1.4-10.2; p=0.018) and generalised anxiety disorder (OR 5.0; 95% CI, 1.7-14.9; p=0.005) compared to matched non-NASH controls (on Patient Health Questionnaire)¹⁸

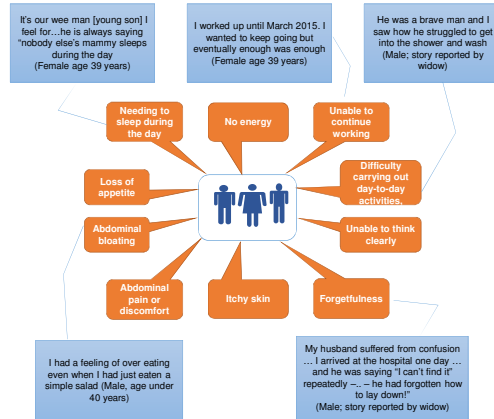
Liver-specific HRQoL (CLDQ)

- NAFLD patients reported significantly lower overall and selected domains scores of CLDQ versus patients with chronic hepatitis (hepatitis B and C)¹²
 - This finding remained significant after controlling for presence of cirrhosis, diabetes, metabolic syndrome, obesity among other comorbidities, suggesting that NAFLD is independently associated with poorer HRQoL¹²
- In a German cohort, NASH patients reported comparable HRQoL impairment to NAFLD patients based on overall mean CLDQ score¹⁹
- Biopsy-confirmed NASH patients reported significant impairment in all six CLDQ domains as compared to normative data from healthy controls (p<0.0001 for all)¹³

Review of patient-reported information

- Patients reported that NASH profoundly impacts many aspects of their lives, including ability to conduct day-to-day activities, personal and social relationships, symptoms, and impact on work (Figure 3)

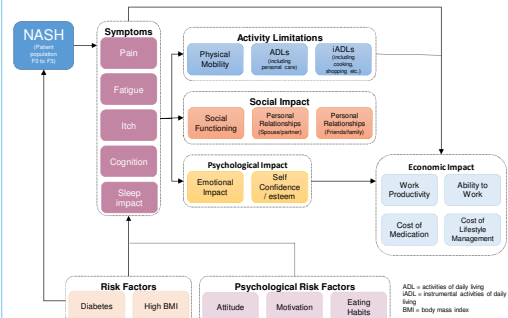
Figure 3. Patient Perspectives on NASH⁶



CONCEPTUAL MODEL FOR NASH

- Clinical experts and patient representatives reviewed the findings and confirmed that these largely matched their views of the patient experience; additional areas of impact raised by patient representatives were economic impact (cost of medication, lifestyle management) and patient behaviour (motivation and eating habits). The results of the reviews were used to develop an initial conceptual model for NASH (Figure 4)

Figure 4. Conceptual Model for NASH



- The experts confirmed that none of the PROMs currently available for use in NASH fully encompass the patient experience as depicted in the conceptual model
- They further highlighted the need for future qualitative work with NASH patients to confirm the above model and initiate the development of a new NASH-specific PROM

DISCUSSION & CONCLUSIONS

- Overall, findings from the current study are consistent with previous reviews^{20,21} and suggest that patients with NASH/NAFLD experience significant impairment in HRQoL
- However, the current review found that patients report other aspects of the disease which are not fully covered by existing PROs
 - SF-36 is a generic instrument not validated for NASH and is unlikely to address all issues relevant to NASH patients
 - CLDQ is used in NAFLD/NASH patients but content validity has not been fully demonstrated for this patient group¹³ and CLDQ-NAFLD was recently developed from CLDQ¹⁴
- Findings from this study reinforce the need to develop a NASH-specific PRO measure based on FDA guidance and NASH patients & experts in order to better quantify the humanistic burden associated with NASH and capture its specific impairment

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