

Review

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A comprehensive review of patient-reported outcomes in metabolic dysfunction-associated steatotic liver disease

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Abstract

The global prevalence of obesity and type 2 diabetes has increased, contributing to an increased worldwide prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD). Currently, one in three adults is affected by MASLD and/or its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), making this liver disease a significant public health challenge. Along with MASH-related cirrhosis, these conditions are poised to become the leading causes of chronic liver disease and liver transplants in the near future. Given the growing burden of MASLD and MASH, it is crucial to understand their impact from the patients' perspective. One way to do this is by assessing patient-reported outcomes (PROs), including health-related quality of life (HRQL). HRQL can be assessed using generic instruments like the short form 36 version (SF-36) and the European quality of life-5 dimensions questionnaire (EQ-5D), or disease-specific tools such as the chronic liver disease questionnaire for nonalcoholic steatohepatitis (CLDQ-NASH). Given the limitations of each instrument, the best approach generally involves using both generic and disease-specific instruments. Evidence indicates that HRQL scores are significantly lower in individuals with MASLD, especially in areas assessing physical activity and the ability to perform daily living tasks. Fatigue and impaired work productivity are also important PROs for those with MASLD/MASH. These decrements in PROs worsen with disease progression but appear to improve with disease regression, including improvements linked to treatment. In this context, measuring PROs enhances the assessment



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of other patient-centric outcomes and provides insights for the healthcare community to develop interventions that could improve both clinical and humanistic outcomes for individuals living with MASLD/MASH.

Keywords: NAFLD, MAFLD, patient-reported outcome (PRO), quality of life

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is a global health problem affecting up to 38% of adults^[1]. As curative treatment for the hepatitis C virus and prevention strategies - such as vaccination and effective viral suppression therapies for hepatitis B - expand globally, MASLD may soon become a leading cause of chronic liver disease^[2]. Since MASLD is tightly related to the metabolic conditions of obesity, insulin resistance, and type 2 diabetes (T2D), its prevalence rises as these conditions become more widespread globally^[2,3].

The more advanced disease state, metabolic dysfunction-associated steatohepatitis (MASH), along with MASH-related cirrhosis, is also increasing, with the most current prevalence rate for MASH noted at 5%, but could be as high as 16% in the general population. Meanwhile, the prevalence of MASH-related cirrhosis among those with MASH has been reported to range between 2% to 7%^[1]. However, these rates may be biased by the recruitment criteria of many studies. Nonetheless, they help to demonstrate the potential extent of MASLD and MASH in society^[1].

MASLD is related to a greater risk for negative outcomes, including an increased risk for all-cause and cause-specific mortality, a greater risk for cardiovascular diseases, and an elevated risk for chronic kidney disease^[4-8]. Among those with MASLD, cardiovascular disease is the leading cause of mortality, followed by extrahepatic cancers (uterine, stomach, pancreatic, esophageal, and colon cancers), and then liver disease. Although these causes of mortality are true for all patients with MASLD, liver disease is the predominant cause of death for those with advanced fibrosis^[9-14]. Among those with hepatocellular carcinoma (HCC) who are listed for liver transplantation, MASH-related HCC is now the number one indication for liver transplantation (LT). However, among all transplant recipients, MASH is the second reason for liver transplant^[14,15,16].

MASLD and MASH are also associated with a decline in patient-reported outcomes (PROs), a term that encompasses health-related quality of life (HRQL) and productivity at work and in their daily activities^[17,18]. In addition, MASLD and MASH have a large fiscal burden resulting from increased use of healthcare resources and lack of productivity at work^[18,19]. Therefore, it is imperative to gain knowledge of the comprehensive burden of MASLD/MASH from the perspectives of individuals, providers, and society. This information can be used to guide clinical practice and policy decisions, potentially improving the comprehensive long-term outcomes for these individuals.

Therefore, in this comprehensive review of PROs in MASLD, using PubMed as our main search engine and the key words PROs, HRQL, and NAFLD, we provide an overview of what PROs are, how they are measured, and describe the impact of MASLD and MASH on PROs.

PATIENT-REPORTED OUTCOMES

The concept of PROs was proposed as a measure to help determine the effectiveness of medical treatment. Since then, the inclusion of PROs has become a mandatory endpoint for clinical trials^[20]. PROs capture what the patient feels about their health without any assistance from anyone, including clinicians or family

members^[20,21]. PROs are multidimensional constructs that cover areas such as: symptoms, pain, fatigue, anxiety, physical functioning, intellectual functioning, and HRQL (comprised of physical, mental, social and bodily functioning as well as overall health domains). Health utilities, defined as a single summary HRQL score, are also important to capture when investigating PROs. Health utilities are used to estimate an individual's health state or their preference for being in a particular health state and are necessary when conducting cost-utility or cost-effectiveness analyses^[22,23].

Given the wide range of concepts and constructs contained within the term PROs, there are different PRO measures (PROMs) or tools used to obtain the necessary data that inform practitioners about the effects of a disease or intervention from the patient's perspective. For HRQL and other subjective measures, such as fatigue, there are self-reported survey measurement tools that are considered to be either generic or disease-specific^[24]. Generic tools are used across diseases and treatments, which enable comparison of scores between different patient groups^[24]. On the other hand, these tools may be less precise when measuring the impact of one particular disease, whereas a disease-specific tool, which is developed with input from people living with the specific disease, may be more responsive to changes over time, whether due to treatment and/or disease progression^[24]. However, disease-specific tools cannot be compared among groups of patients with different diseases. As such, many studies will use both a general (generic) and a specific tool for the disease of interest to overcome the limitations of both types of surveys. Although there are objective measures of physical function, such as hand grip strength, treadmill testing, or a six-minute walk test^[25], this review focuses solely on self-reported survey tools.

In this context, one very important concept when measuring PROs over time is understanding what changes in PRO scores are considered clinically significant, potentially consequential, and meaningful for patients^[26,27]. The minimally clinically important difference (MCID) is the terminology used to denote this change^[27]. Therefore, knowing the MCID for each tool is imperative, especially for clinical trials, so that the true effect of an intervention from the patient or individual's perspective can be appreciated^[28]. In general, MCIDs are determined for each PRO using a structured approach. The Food and Drug Administration (FDA) suggests that the MCID can be calculated by subtracting the mean change in scores of patients who did not improve from the mean change in scores of patients who did improve, along with the 95% confidence interval. This method is sometimes referred to as the anchor-based within-patient change^[28]. Alternatively, others estimate the MCID based on a score change ranging from $\pm 4\%$ to $\pm 5\%$ ^[29]. This approach is less robust and may only give a rough assessment of the clinically meaningful change in the scores.

When selecting a measurement tool, one needs to consider several factors, including the tool's appropriateness for the study, its reliability, validity, and responsiveness to change, its MCID, its feasibility in practice, and the ease of score interpretation^[17]. In the following sections, we present some of the more commonly used HRQL tools, fatigue assessment tools, and work/productivity assessment tools for individuals with MASLD.

MEASUREMENT TOOLS

HRQL measurement

Short form 36 version 2

Worldwide, the Short form 36 version 2 (SF-36v2) is the most commonly used generic HRQL instrument^[30]. It consists of 36 questions that assess eight areas: physical functioning, social functioning, role-physical, role-emotional, mental health, vitality, bodily pain, and general health perceptions. The SF-36v2 also provides two summary scores: one for physical functioning (physical component score, or

PCS) and one for mental health (mental component score, or MCS). Each domain is summed and then transformed to a score that ranges from 0-100, where 0 indicates the worst HRQL and 100 indicates the best HRQL. The PCS score and MCS scores range from 0-50, with 0 again indicating the worst HRQL and 50 indicating the best score. As such, higher scores indicate less impairment and better HRQL. The SF-36V2 has been translated into numerous languages and has population norms for score comparisons^[30].

European quality of life-5 dimensions questionnaire

The European quality of life-5 dimensions questionnaire (EQ-5D) is also a commonly used generic HRQL instrument^[31-33]. The EQ-5D has five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these areas is scored using a Likert scale ranging from 1-3, where 1 indicates no problems, 2 indicates some problems, and 3 indicates extreme problems. Lower scores indicate better HRQL and less impairment^[31-33]. The EQ-5D is also often used to create health utility scores. These generate quality-adjusted life years (QALYs), which are used in cost-utility or cost-effectiveness models^[33].

Chronic liver disease questionnaire-NASH

The chronic liver disease questionnaire (CLDQ) tool was developed in 1999 to measure HRQL among those with chronic liver disease, making it a liver disease-specific tool. The CLDQ has 29 questions that encompass six areas (abdominal symptoms, activity/energy, emotional health, fatigue, systemic symptoms, and worry). Each area is scored on a scale from 0-7. Higher scores indicate better health and fewer symptoms^[34]. Over the past two decades, the original CLDQ tool has been refined to specifically measure HRQL related to different liver diseases, such as NAFLD, NASH, HBV, HCV, primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC)^[35-40]. Refinement of the CLDQ was completed by obtaining additional input from patients with the liver disease of interest through focus group and individual interviews, followed by item reduction, factor analysis, and psychometric assessments to evaluate validity, responsiveness, and reliability^[41].

For the purposes of this review, we provide an in-depth analysis of the CLDQ-NASH. The CLDQ-NASH consists of 36 items, retaining 25 of the original 29 questions and the six domains described above. The additional questions better capture the effects of obesity and depression conditions that are more prevalent in those with MASLD and MASH. CLDQ-NASH is now a fully validated instrument, widely used in a large number of clinical trials, as well as in national and global registries^[37,40].

Liver disease quality of life questionnaire and the short form

The liver disease quality of life questionnaire (LDQOL) and its short version (SF-LDQOL). The LDQOL was developed in 2000 using the SF-36v2 as its foundation. An additional 75 disease-specific items were added and then grouped into 12 areas (liver disease-related symptoms, liver disease-related effects on activities of daily living, concentration, memory, sexual functioning, sexual problems, sleep, loneliness, hopelessness, quality of social interaction, health distress, and self-perceived stigma of liver disease)^[42]. However, given the time required to complete this survey, a shorter version of the LDQOL (the SF-LDQOL) was developed in 2008 to reduce the time of survey completion^[43]. The SF-LDQOL retains the SF-36v2 questions, but now includes only 36 disease-specific items and nine areas covering symptoms of liver disease, effects of liver disease, memory and concentration, sleep, hopelessness, distress, loneliness, liver disease stigma, and sexual functioning problems. Investigators determined that the SF-LDQOL took a mean of 18 (±9) min to complete, compared to 38 (±20) min for the LDQOL 1.0^[42,43]. [Table 1].

Fatigue

Functional assessment of chronic illness therapy-fatigue

The functional assessment of chronic illness therapy-fatigue (FACIT-F) scale evaluates different aspects of

fatigue in individuals with chronic illness^[44]. Using 13 questions, the impact of fatigue is measured over four areas: physical well-being, social/family well-being, emotional well-being, and functional well-being. Each question is answered on a 5-point Likert scale that ranges from 0 to 4, where 0 indicates “not at all” (the issue does not bother them) and 4 indicates the issue bothers them “very much”. To achieve the overall score, all the answers are added together with a maximum score of 52. Higher scores represent better functioning and less severe fatigue. A score of less than 40 indicates the presence of clinically significant fatigue that interferes with one’s daily activities. The FACIT- F has been validated in numerous countries and languages. Population norms for different countries are also available for comparison^[44].

Fatigue severity score

The fatigue severity score (FSS) was developed to measure fatigue for different conditions that are chronic in nature^[45]. It is a 9-item questionnaire that evaluates the impact of fatigue on daily functioning, motivation, physical activity, work, family, and social life. Respondents are asked to score the severity of their fatigue symptoms using a Likert scale ranging from 1 (completely disagree with the statement) to 7 (completely agree with the statement). A higher score indicates more fatigue and a score > 36 indicates a high level of fatigue^[45].

Fatigue impact score

The fatigue impact score (FIS) can also be used to measure fatigue in those with a chronic disease or condition^[46]. The FIS contains 40 questions across three domains: cognitive, physical, and psychosocial functioning. Each question is scored on a 5-point Likert scale ranging from 0 (no problem) to 4 (an extreme problem). The maximum score is 160 and higher scores demonstrate greater fatigue^[46]. [Table 1].

The work productivity and activity impairment-specific health problem

The work productivity and activity impairment-specific health problem (WPAI-SHP) measures the impact of individuals’ health state on their ability to work productively and participate in activities of their choice^[47]. The WPAI produces scores in four areas: absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment / absenteeism plus presenteeism) and activity impairment. The WPAI:SHP consists of six questions: five related to work productivity and one related to activity impairment. Higher scores indicate higher levels of impairment^[47].

PATIENT-REPORTED OUTCOMES DATA IN MASLD

Studies using the aforementioned tools have reported that those with MASLD experience significant impairment in their HRQL, particularly in areas related to physical activity/functioning. They also report higher levels of fatigue and decreased work productivity in terms of presenteeism, compared to those without MASLD^[48-54]. Disease progression, including advanced fibrosis, cirrhosis and hepatocellular cancer, is an independent predictor of decreased HRQL and higher levels of fatigue^[49-54]. In fact, a recent study found that reports of fatigue were actually prognostic for adverse outcomes (liver events and mortality) among those with MASLD and MASH^[53,55]. Additionally, depression rates are higher in patients with MASLD than in the general population^[56].

Currently, the first-line treatment for MASLD remains diet and exercise; however, implementation of an effective intervention can be complicated by the level of fatigue present^[57]. Therefore, it is important to have a better understanding of fatigue and the drivers of fatigue among those with MASLD. Fatigue is a multidimensional state that is made up of both a peripheral component (peripheral fatigue) and a central

Table 1. Measurement tools for assessing patient-reported outcomes in patients with MASLD/NAFLD

Name of tool	Health domains measured	Items	Strengths or limitations	Generic or disease-specific
SF-36v2 ^[30]	-Measures 8 domains: physical functioning, social functioning, role-physical, role-emotional, mental health, vitality, bodily pain, and general health, and two summary scales of physical composition and mental composite scores	36 items	-Most widely used tool -Established population norms for comparison -May not be sensitive to disease change	Generic
EQ-5D ^[31-33]	-Measures five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression	Each area with three levels of functioning	-Brevity and easy administration -Disease-specific patient-reported outcome questionnaire is required to better encompass the symptoms of NAFLD/MAFLD	Generic
CLDQ ^[34]	-Measures six domains: (1) fatigue; (2) activity; (3) emotional function; (4) abdominal symptoms; (5) systemic symptoms; and (6) worry	29 items using a Likert scale of 1-7	-Widely used and validated tool to measure health-related quality of life -Translated into many languages -Cannot be compared with other chronic diseases	Disease-specific
CLDQ-NAFLD, CLDQ-NASH ^[37, 40]	-Measures six domains: (1) abdominal symptoms; (2) activity/energy; (3) emotional health; (4) fatigue; (5) systemic symptoms; and (6) worry	36 items: 29 items from CLDQ and 7 new items to better capture the impact of fatigue in the NAFLD population	Strengths: -Excellent internal consistency, face validity, content validity, and test-retest reliability -Further validation is needed in NAFLD/NASH cirrhosis -Cannot be compared with other chronic diseases	Disease-specific
LDQOL ^[42]		SF-36v2 questions + 75 disease-specific items	-Very thorough assessment -Takes a lot of time (approximately 40-60 min) to complete, making it impractical for use in a clinical setting	Specific
SF LDQOL ^[43]	-Measures nine domains: symptoms of liver disease, effects of liver disease, memory/concentration, sleep, hopelessness, distress, loneliness, stigma of liver disease, and sexual functioning problems	SF-36v2 questions + 36 disease-specific items	-Retained the validity and reliability of the LDQOL but time to complete was reduced by 50% (20-30 min) -Still requires a long time to complete	Specific
FACIT-F ^[44]	-Measures four primary quality of life domains: physical well-being, social/family well-being, emotional well-being, and functional well-being, and the effect of fatigue on these domains	16 questions scored (0-4 Likert scale)	-Formatted for ease of self-administration for use with special populations such as the elderly and those living in rural areas -Takes 4-6 min to complete -Appropriate for use in patients with a variety of chronic health conditions and in the general population -Interviewer training is needed to minimize bias against patient responses	Disease-specific
FSS ^[45]	Measures the severity of fatigue and its effect on a person's activities and lifestyle in patients with a variety of disorders	9 item scale, scored on a 7-point scale	-Item formulated as statements about the fatigue experience itself, what causes fatigue and how fatigue interferes with daily life.	Generic, but can be modified to disease-specific
FIS ^[46]	Evaluates the effect of fatigue on three domains of daily life: cognitive functioning, physical functioning, and psychosocial functioning	Contains 40 questions with a 5-point Likert scale	-Easy to administer -Limitation is the length of the questionnaire	Generic
WPAI-SHP ^[47]	-Work productivity and activity: presenteeism and absenteeism -Instrument- Specific Health Problem	Consists of six questions: five questions for work productivity and one question on normal daily activities	-7-day recall period -Sufficient validity, reliability, responsiveness, and appropriate interpretation standards to assess the impact of disease on WPAI	Disease-specific

SF-36v2: Short form 36 version 2; CLDQ: chronic liver disease questionnaire; NAFLD: non-alcoholic fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease; NASH: nonalcoholic steatohepatitis; EQ-5D: European quality of life-5 dimensions questionnaire; HRQL: health-related quality of life; LDQOL: liver disease quality of life; SF-LDQOL: short form liver disease quality of life; FACIT-F: functional assessment of chronic illness therapy-fatigue; FSS: fatigue severity score; FIS: fatigue impact score; WPAI-SHP: work productivity and activity impairment-specific health problem.

component (central nervous system, CNS)^[25,58]. Liver disease-related fatigue is considered a pathological state, as it does not improve with rest after exertion or with treatment of underlying conditions, such as anemia. In fact, in liver-related fatigue, the central fatigue component may be dominant due to the presence of the inflammatory milieu associated with obesity and MASLD. This liver inflammation sets off a cascade of events affecting the neural, humoral, and immune-mediated networks, which change the neurotransmission within the CNS. Central fatigue is typically characterized by a lack of motivation, difficulty sleeping, depression and anxiety, social withdrawal, and cognitive impairment, often described as brain fog. While central fatigue may be more dominant, peripheral fatigue may be present, also manifesting as the decreased ability to be physically active despite having the capacity to do physical activity, particularly evident in those without advanced steatosis or fibrosis^[25,53,58-62].

Obesity and metabolic abnormalities may also play a role in driving other fatigue mechanisms such as autonomic dysfunction, mitochondrial abnormalities, and other inflammatory mechanisms. Additionally, studies have shown that being female and older are more common predictors of lower PRO scores^[50].

Despite these significant findings obtained via measurement tools, most individuals with MASLD remain unaware that many of their reported symptoms of fatigue, stomach pain, anxiety, depression, poor focus and memory, and impaired sleep are related to their liver disease^[50]. This underscores the importance of assessing PROs during a clinical visit to prescribe individualized treatment. Furthermore, having baseline measurements in these areas can also help practitioners evaluate prescribed treatment and intervention outcomes, as studies have shown that improvement in PROs can indicate disease regression, whereas worsening of PROs may signal disease progression^[63,64]. This suggestion is especially important now that medication is available for those most at risk for MASLD-related adverse outcomes (MASLD with fibrosis stage 2 and stage 3)^[64]. In clinical trials, patients who experienced fibrosis regression without disease progression demonstrated improved HRQL, especially in the domains of physical functioning and worry^[63,64].

PATIENT-REPORTED OUTCOMES AND STIGMA

Although stigma has been studied in other liver diseases, there is a paucity of research on stigma and its effects among those with MASLD^[65-68]. Two recent studies were undertaken to begin filling this gap of knowledge^[69,70]. The first study explored the perception of stigma among providers and patients, where investigators found a discrepancy between the NAFLD-related terms that patients and providers felt were stigmatizing. Specifically, patients reported stigma related to the terms “obese” and “overweight,” but not to NAFLD. In contrast, physicians felt the term “fatty” was stigmatizing, as was “non-alcoholic,” especially in the Middle East and North Africa regions. However, only a few felt that the term “steatotic liver disease” would be stigmatizing^[69]. As such, given the name change from NAFLD to MASLD, future research is needed to determine whether the name change will reduce stigma among patients and providers.

The second study explored the relationship between stigma and HRQL among 2,000 patients from around the world with MASLD. Those who reported stigmatization due to NAFLD or obesity had substantially lower HRQL scores. Patients’ self-blame for their liver disease also contributed to their lower HRQL.

Research work must focus on helping patients with MASLD overcome self-blame to improve their HRQL and engage in their prescribed treatments^[70].

PATIENT-REPORTED OUTCOMES IN LIVER TRANSPLANT RECIPIENTS

It is important to note that issues related to the post-transplant status of patients with liver disease can be very different from those associated with chronic liver disease. In the United States, the number of patients receiving liver transplants continues to increase each year, with over 10,000 patients receiving a LT in 2023. In addition, the one-year and five-year survival rates are improving dramatically (1-year: 90%, 5-year: 70%). Several recent studies examining survival post-liver transplant for those with MASLD have confirmed that their survival was similar to those transplanted for other liver diseases^[71,72]. Nevertheless, post-transplant co-morbid metabolic diseases, such as obesity and T2D, are common in those transplanted for MASH, and these factors can negatively impact patients' HRQL scores even after transplant^[72-74]. Although there is evidence of substantial improvement in HRQL post-LT, PROs specifically for post-transplant patients with MASLD have not been fully investigated^[75].

FUTURE RESEARCH

As the understanding of MASLD and its spectrum of disease evolves, investigating PROs along this continuum will be essential to providing more nuanced care. Although data from the first medication-based regimen for MASH suggest not only histologic improvement but also improvement in PROs, other regimens are in clinical trials and may show additional benefits that will be important to study. Although documenting the improvement of PROs in clinical trials is important, understanding the long-term effectiveness of these regimens in real-world practice is critical and represents another important area for further study. Finally, studies investigating PROs before and after LT in patients with MASH/NASH and MASH/NASH-related HCC are also needed.

CONCLUSION

In this review, we defined PROs and summarized the features of some of the more commonly used instruments for assessing PROs in individuals with MASLD. With the use of these tools, MASLD/MASH has been shown to have a significant negative impact on patients' PROs, especially in the advanced stages of the disease. In fact, study findings indicate that individuals with MASLD/MASH experience worse physical and mental health, increased fatigue, and decreased productivity at work compared to the general population. These findings challenge the perception that MASLD is an asymptomatic disease or one characterized by only vague complaints of fatigue, anxiety and/or abdominal discomfort. Additionally, assessment of fatigue through a validated self-report tool is crucial for patients with MASLD/MASH, as the presence of fatigue has been shown to have prognostic value. Despite this knowledge, areas of investigation remain, especially the long-term PRO scores for individuals receiving treatment with resmetirom and other regimens expected to be approved in the future, as well as for those who have undergone LT.

DECLARATIONS

Authors' contributions

Concept design, critical review of the manuscript: Sapmaz A

Manuscript writing and editing: Paik A

Study design, manuscript writing, and critical review of the manuscript: Henry L

Critical review of the manuscript: Younossi ZM

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Younossi ZM has received research funding and/or served as a consultant to Intercept, Cymabay, Boehringer Ingelheim, BMS, GSK, Novo Nordisk, AstraZeneca, Siemens, Madridgal, Merck, and Abbott. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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