Health related quality of life in people with advanced chronic liver disease

James G. Orr¹, Tara Homer², Laura Ternent², Julia Newton¹, Calum J. McNeil¹, Mark Hudson¹, David E.J. Jones¹,⇑

¹Institute of Cellular Medicine, Newcastle University, UK; ²Institute of Health and Society, Newcastle University, UK

Summary

Cirrhosis has a long natural history with considerable symptomatic impacts, particularly in advancing disease. Measuring health related quality of life (HRQOL) in liver disease provides detail about the nature and extent of its effects on individuals. Understanding the drivers of impaired HRQOL can help identify targets for improvement through new treatments or health systems service delivery. Evaluation of novel therapies which target symptomatic improvement, should be done with suitable outcome measures, including HRQOL assessment. In this article, we provide an overview of HRQOL in advanced liver disease for the clinician. A clear description of the important HRQOL tools is given alongside a discussion of the factors, which are known to contribute to impaired HRQOL in advanced liver disease.

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Introduction and clinical context

The burden of liver disease is increasing, largely due to the combined impacts of alcohol related liver disease (ARLD) [1], non-alcoholic fatty liver disease (NAFLD) [2] and viral hepatitis [3,4]. Liver disease is often sub-clinical until more advanced disease is established, resulting in an increasing incidence of cirrhosis in many countries [5]. Medical approaches to cirrhosis, such as screening for hepatocellular carcinoma (HCC) and variceal surveillance, often focus on risk reduction. While these strategies, targeted to clinical factors, are clearly important, they do not consider patient factors such as health related quality of life (HRQOL). Measuring HRQOL can quantify the impact of a disease and its treatment on the individual and is increasingly recognised as an important outcome in chronic diseases such as cirrhosis.

Compensated cirrhosis is associated with a median survival of 12 years [6] meaning that even patients who go onto liver transplantation will have lived for considerable periods of time with advanced disease. Evaluation of treatments for cirrhosis usually consider clinical end points such as mortality rates, biochemistry results or the incidence of complications, but these do not consider patients’ values. Measuring HRQOL can reflect the emotional, physical and lifestyle implications of medical conditions and treatments, which are typically more important to patients than traditional outcomes [7].

An understanding of the factors which drive impaired HRQOL in advanced liver disease should allow identification of targets for novel therapies. Increased awareness of HRQOL should enable provision of services with a balance between clinical and patient factors. Many treatments for advanced liver disease aim to alleviate specific symptoms rather than improving long term outcomes; such treatments are therefore best evaluated with a robust assessment of HRQOL.
Measuring health-related quality of life

There are a variety of methods available for measuring HRQOL, which can reflect both objective and subjective aspects. Objective constructs can measure an individual’s ability to carry out specific tasks or activities, while subjective measures relate to the perceived impact of health status on wellbeing [8]. These two approaches are complimentary: while objective measures tend to be easier to analyse, subjective measures relate to the patient experience more closely. Generic measurement scales provide an overview of HRQOL, usually taking into account physical, mental and social aspects of the health status. An advantage of generic scales is that they allow the relative impact of different diseases to be studied, which can be useful to health policy makers. In addition, extensive normative data allow comparisons with the general population. The main disadvantage is a lack of sensitivity to clinically important changes. For this reason, generic scales are often combined with disease-specific scales, which measure clinical and social factors directly relevant to the condition being studied. Disease-specific scales should show how disease severity, clinical outcomes and the effects of treatment affect HRQOL. Domain-specific scales, which focus on one specific area of interest, such as sleep or fatigue, are sometimes also added. Clearly, the additional detail, which can be achieved using more tools, must be balanced against participant burden [9].

Questionnaire-based tools frequently use categorical Likert scales with a series of ordered responses (e.g., never, rarely, sometimes, most of the time, always), although dichotomous categorical questions (e.g., yes/no) or visual analogue scales (VAS) are sometimes used. Measurements of HRQOL can be patient-derived or derived from non-patient populations, such as physicians. While there are theoretical advantages from using non-patient populations, such as reduced subjectivity [10], it is generally recognised that patient-derived HRQOL measurements are more valuable [9].

Health utilities are subtly different from HRQOL indices and are used to assign a single value, which represents a preference for a specific state of health [11]. In practice, utility scores fall between 0 and 1, where 0 corresponds to death and 1 to perfect health, although in some cases a negative score can be assigned to health states considered to be worse than death (e.g., unconsciousness) [12]. Utility values are used to calculate quality adjusted life years (QALYs), which combine length of life with quality of life such that a year of full health is equal to 1 QALY [13]. QALYs allow comparisons to be made between different conditions and are widely used in health technology assessments. There are various different techniques to derive utility values, described elsewhere [13,14].

HRQOL tools used in studies of chronic liver disease

The wide variety of tools can make it difficult to assimilate the literature on HRQOL, not least because of the variation in domains measured and scales used. The generic and disease-specific tools most commonly used in studies of HRQOL in liver disease are summarised in Tables 1 and 2 respectively and a brief description is given below to help contextualise the subsequent literature review.

SF-36 is the most widely used generic tool and was derived from the larger 116-item measures of quality of life core survey. It consists of 36 questions, split into eight domains with two summary scores: the physical component summary (PCS) and the mental component summary (MCS), as illustrated in Fig. 1. In the most recent version, SF-36v2, all scores are expressed as T-scores, normalised to the 2009 data from the general U.S. population, with a score of 50 corresponding to the U.S. mean and 1 standard deviation equal to 10. Preference-based health utilities can be calculated using the SF-6D algorithm [15], which uses 11 items across all domains other than general health to generate a utility score on a 0.0–1.0 scale [16]. The sickness impact profile (SIP) has 136 questions, which make up 12 scales in three dimensions. Higher scores represent greater impairment and all 12 scales are summarised by an overall SIP score on a 0–100 scale [17]. Another commonly used generic measure is the Nottingham health profile (NHP), which consists of two parts: part one comprises 38 yes/no questions in six “subareas”, each of which is scored on a 0–100 scale, with higher scores indicating poorer health status; part two assesses which of seven areas of a patient’s life are affected by health problems [18,19].

In addition to these generic tools, disease-specific measures have been developed, which aim to measure more accurately the specific impacts of liver disease on HRQOL. The most widely used liver disease-specific measure is the chronic liver disease questionnaire (CLDQ), which comprises 29 questions split into six domains. Domain scores and an overall score are presented on a 1–7 scale with higher scores representing better HRQOL [20]. The liver disease quality of life (LDQOL) measure uses SF-36v2 as a generic core and adds 12 liver-specific scales comprising 75 questions. All scales are scored on a 0–100 scale with higher values representing better HRQOL [21]. A short form version, SF-LDQOL, has also been developed with 36 liver-specific questions split into nine scales [22]. Finally, the liver disease
Review

Table 1. Generic HRQOL tools used in chronic liver disease.

<table>
<thead>
<tr>
<th>Tool</th>
<th>Format</th>
<th>Structure</th>
<th>Scoring</th>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>SF-36</td>
<td>36 Likert items</td>
<td>2 summary scores: Physical Component Summary and Mental Component Summary 8 domain scores: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, Mental Health</td>
<td>• All domains and summary scores expressed as T scores where 50 equal to mean US normative scores and 10 equal to one standard deviation. • Higher scores correspond to better HRQOL</td>
<td>• Most widely used generic measure • Multiple foreign language versions • Allows comparison with other diseases • Utility scores can be derived using SF-6D • Norm based scoring • Shorter forms available (SF-8 and SF-12)</td>
<td>• License fee payable to use scoring algorithms • US norms used which may differ from normative data from other populations</td>
</tr>
<tr>
<td>SIP</td>
<td>136 dichotomous items</td>
<td>12 domains in 3 dimensions: 1. Independent categories: sleep and rest, eating, work, home management, recreation and pastimes. 2. Physical dimension: ambulation, mobility, body care and movement. 3. Psychosocial dimension: social interaction, alertness behaviour, emotional behaviour, communication</td>
<td>• All domains and overall score expressed on 0-100 scale. Higher scores correspond to greater impairment of HRQOL</td>
<td>• Widely used • Allows comparison with other diseases</td>
<td>• Can be burdensome for respondents • License fee payable to use • No authorised foreign language translations</td>
</tr>
<tr>
<td>NHP</td>
<td>45 dichotomous items</td>
<td>6 domain scores: energy level, pain, emotional reaction, sleep, social isolation, physical abilities 7 life areas affected: occupation, jobs in the home, home life, social life, sex life, hobbies, holidays</td>
<td>• Domain scores expressed on 0-100 scale. Higher scores correspond to greater impairment of HRQOL. • Life areas affected: yes/no response</td>
<td>• No license fee • Quick to complete • Validated foreign language versions</td>
<td>• Less widely used in liver disease than other generic tools</td>
</tr>
</tbody>
</table>

SF-36, short form-36; SIP, sickness impact profile; NHP, Nottingham health profile.

symptom index 2.0 (LDSI) is made up of 18 items measuring the severity and impact on daily activities in nine areas [23].

Health related quality of life in cirrhosis

Before considering HRQOL in cirrhosis, it is useful to first look at the impact of the less advanced disease. Studies of chronic liver disease have consistently shown that HRQOL is significantly poorer in both cirrhotic and non-cirrhotic patients than healthy controls [24] or normative data [25]. Importantly, cirrhosis is associated with poorer HRQOL than non-cirrhotic chronic liver disease when measured by either CLDQ [25] or SF-36 [26]. Perhaps unsurprisingly, studies comparing cirrhotic patients to the general population have demonstrated significantly impaired HRQOL in cirrhosis [27,28] and a study comparing cirrhotic patients with their carers showed that patients’ HRQOL scores were significantly poorer across a range of measures [29].

While impaired HRQOL might be expected, given the clinical features of cirrhosis, it is helpful to characterise the extent and nature of the impairment. Closer analysis of the factors underlying poor HRQOL in cirrhosis should provide potential targets for novel therapies and help detail outcome measures, which could be used to assess future developments.

Influence of liver disease severity on HRQOL

How does disease severity impact on the degree of HRQOL impairment in chronic liver disease? In a cohort of 1103 chronic liver disease patients, Child-Pugh score (CPS) class B or C cirrhosis was associated with significantly poorer SF-36 scores than class A, but CPS classes B and C were similar [26]. This pattern has also been demonstrated by other studies [28,30] while three studies found significant differences only in some domains and in the PCS but not the MCS [20,31,32], although these were smaller studies. One study found the CPS to be one of two variables which correlated independently with the PCS [33]. The CPS was also identified as an independent variable predictive of poor HRQOL (>1SD worse than controls) in the PCS and 4 domains of the SF-36 (PF, RP, VT, SF) as well as the energy and physical mobility domains of the NHP [27].

Interestingly, one study showed that PCS deteriorated with advancing CPS but multivariate analysis found that the CPS was not an independent predictor of PCS [34]. However, all patients included in this study had ascites; given that ascites is one of the five parameters used to calculate the CPS, this observation might suggest that ascites is the main driver of impaired HRQOL seen with increasing CPS. Indeed, severe ascites was an independent predictor of impaired PCS while serum bilirubin, albumin and prothrombin time (PT), three of the four other CPS parameters, were not [34].

CLDQ assessments of HRQOL show a similar pattern to SF-36 with respect to the CPS, with CLDQ scores of CPS class B and C cirrhosis significantly worse than CPS class A, but the CLDQ did not seem to discriminate between CPS class B and C [20,28,30].

An alternative disease-specific measure, the LDQOL, may better differentiate between CPS classes. Two studies demonstrated significant associations between the CPS class and LDQOL in the following domains: effects of liver disease, sexual functioning and sexual problems [21,32], while the symptoms of liver disease and stigma of liver disease domains were also significantly associated in the latter study [32]. In addition, the health utilities index HUI-2 showed significantly poorer utility scores with...
increasing severity (non-cirrhosis vs. CPS A vs. CPS B vs. CPS C) with a marked difference between CPS B and C (0.71 ± 0.27 vs. 0.46 ± 0.22) [25].

Data on the relationship between the model for end stage liver disease (MELD) score and HRQOL are limited, partly because MELD was not widely used until 2002 [35]. In a Polish study of 87 cirrhotic patients, significant correlations were found between the MELD score and both summary scores and five domains of SF-36 [36]. Kanwal et al. found a significant correlation between the PCS and MELD score, but only 8% of patients had MELD scores >20 and the correlation was weaker than that seen with the CPS [32].

One study reported significant differences between MELD <15 and >15 in four domains of SF-36 (SF, RP, BP, and GH) with no summary score data [37]. In a study of 150 patients awaiting liver transplantation, there was a weak correlation between both SF-36 and CLDQ scores and MELD but univariate analysis showed that MELD was not a predictor of either score [38].

There is evidence that LDQOL responds to the MELD score with significant associations seen with the effect of liver disease, health distress, stigma of liver disease and sexual function domains [32]. In addition, the Brazilian-Portuguese translation of LDQOL reflects differences in HRQOL when comparing MELD scores less than or equal to 15 with scores greater than 15 [37,39].

**Influence of liver disease aetiology on HRQOL**

A large number of studies have looked at how HRQOL differs between liver diseases. A German study of non-cirrhotic patients showed interesting differences in the pattern of impairment as measured by SF-36, with PBC patients scoring lowest on the PCS while patients with HCV had the lowest MCS scores [40]. These findings are consistent with other work which found fatigue to be a key factor in PBC [41], while HCV has been shown to be associated with depression [42]. By contrast, Younossi et al. showed that in cirrhosis PCS was similar between cholestatic diseases and viral hepatitis but poorer with other hepatocellular diseases [30]. Another US study compared NAFLD, chronic HBV and HCV, showing that NAFLD patients had significantly poorer CLDQ scores than patients with HBV in five of the six domains and in the overall score. HCV scores were better than NAFLD in two domains (emotional and systemic symptoms) but worse than HBV in two domains (abdominal symptoms and activity). A far greater proportion of patients with HCV had cirrhosis but in multivariate analysis the greater impairment in HRQOL seen with NAFLD persisted after correction for cirrhosis as well as other factors such as diabetes, obesity and gender [43]. The same authors also showed health utility scores SF-6D and HUI-2 to be significantly poorer with HCV than HBV in multivariate analysis [44].

A study which compared patients with cirrhosis of various causes, also found that HRQOL was most impaired in HCV, with poorer scores in seven of the twelve LDQOL domains and two of the eight SF-36 domains [37]. However, data for other aetiologies were not considered separately but instead combined into one “non-HCV cirrhosis” category, likely due to small numbers. A larger study, which included 761 cirrhotic patients, found that patients with NAFLD had significantly lower SF-36 PCS and PF than patients with ALD, cholestatic liver disease or viral hepatitis [26]. On the other hand, two studies found no difference in HRQOL between aetiologies [31,33].

Therefore, the evidence of the impact of liver disease aetiology on HRQOL is conflicting and there is no consistent pattern which
will be partly due to the heterogeneity in study design. However, there is evidence that HRQOL is impaired in all aetiologies but the pattern of impairment may vary between different aetiologies. Chronic HBV infection appears to be associated with better HRQOL than other aetiologies, while HCV and NAFLD are associated with poorer HRQOL.

**Influence of hepatic decompensation on HRQOL**

While clinical experience of treating patients with advanced liver disease suggests that patients with decompensated disease have poorer HRQOL, it is useful to explore the specific ways in which patients are affected by decompensation. A study from the US found that the total SIP score was worse in decompensated cirrhosis than in compensated cirrhosis, as were several domains of the SIP. A computerised tool, PROMIS-CAT, was also used, which showed greatest impairment in social functioning, physical functioning, and pain domains [29]. A Dutch study also showed that patients with decompensated cirrhosis had poorer HRQOL using SF-36, the multidimensional fatigue index-20 (MFI-20) and LDSI. Interestingly, the authors describe a subgroup of patients as “reversed decompensated cirrhotic patients” who had a previous episode of decomposition, but who were compensated at the time of the study, for example following treatment of ascites with diuretics. The HRQOL of these patients was comparable to patients with compensated cirrhosis and hence they were classified as compensated cirrhosis [45]. This suggests that resolution of decompensation is associated with an improvement in HRQOL to levels seen in compensated disease, implying that there is potential to vastly improve patient HRQOL through effective treatment of decompensation. This perhaps “raises the bar” in decompensated disease, particularly in the management of ascites or hepatic encephalopathy (HE), giving rise to the concept that a structured approach could be taken to improving HRQOL in advanced liver disease through the specific targeting of individual complications such as ascites and encephalopathy.

**Influence of ascites on HRQOL**

In a study of 544 patients with cirrhosis including 199 patients with ascites, Marchesini et al. showed significant differences in most SF-36 and NHP domains when comparing patients without ascites to those with either mild-to-moderate or severe ascites. Ascites was found to be an independent predictor of poor HRQOL in three SF-36 domains (bodily pain, general health and mental health) but of neither summary score nor any of the NHP domains [27]. On the other hand, in a study of 523 patients, all of whom had ascites, the presence of severe (tense) ascites was found to be an independent factor predictive of impaired PCS in multivariate analysis [34]. In a study of 160 cirrhotic patients, the 69% with a history of ascites had significantly poorer SF-36 PCS, but MCS was similar to those without ascites [31]. This was confirmed by a Swedish study, which also assessed GI symptoms using the GI symptoms rating scale. Significantly more severe GI symptoms were seen with ascites in the following domains: abdominal pain, indigestion, constipation and eating dysfunction [46].

Therefore, ascites appears to affect HRQOL predominantly through physical impairment, driven at least partly by GI symptoms, although one study did report significant impairment of the SF-36 MCS as well as the PCS [47]. Ascites also associates with patients’ self-rating of disease progression over the preceding year [27], suggesting that the development of ascites signals to patients a deterioration in their condition, potentially further impacting HRQOL.

Treatment of refractory ascites with transjugular intrahepatic portosystemic shunt (TIPS) insertion might be expected to lead to considerable gains in HRQOL, for example through reduced abdominal symptoms, fewer hospital admissions and improved body image. However, on one hand a randomised controlled trial (RCT) found that HRQOL was similar in both the TIPS and control groups, due to the development of post TIPS HE in some patients, offsetting the improvements due to reduced ascites [48]. On the other hand, meta-analyses have reported a survival benefit [49,50], suggesting that additional multi-centre studies of TIPS in refractory ascites, including HRQOL assessment, would be useful.

**Influence of hepatic encephalopathy (HE) on HRQOL**

One small study compared 18 patients with previous overt HE (OHE) with 57 patients without a previous episode. Patients with previous OHE had significantly worse SF-36 PCS and MCS and this variable was found to be an independent predictor of the MCS. However, the presence of minimal HE (MHE) affected only one domain of SF-36 (physical functioning); PCS and MCS were unaffected [47]. Similar findings were reported by another study, which assessed the impact of MHE on HRQOL in 77 cirrhotic patients without a history of OHE. No significant differences were found in any of the CLDQ or SF-36 domains or summary scores when comparing patients with MHE to those without [36].

By contrast, a study of 160 patients with cirrhosis undergoing assessment for liver transplantation showed that patients with either MHE or OHE had lower MCS scores than patients without HE. Interestingly, the presence of OHE most greatly affected the PCS [31]. Another study of 106 patients with cirrhosis, excluded patients with previous OHE and showed patients with MHE had significantly poorer scores in all SF-36 domains than those without MHE. However, CLDQ scores were similar between these two groups, with the exception of the abdominal symptoms domain [28]. Baseline data from an RCT of lactulose for MHE showed that patients with MHE had significantly poorer SIP scores in all but one domain. Treatment with lactulose improved total SIP scores, which correlated with improved psychometric test performance. In addition, in multivariate regression analysis, MHE was the only variable found to be significantly related to HRQOL (PCS, varices, aetiology and education status were the other variables tested) [51], consistent with an earlier study [52]. In an RCT of rifaximin...
in MHE, baseline data showed that patients with MHE had significantly impaired HRQOL across all 12 scales and in the overall score of the SIP. In addition, treatment with rifaximin improved both SIP scores and psychometric tests for MHE [53]. Another RCT of rifaximin evaluated its use in the maintenance of remission following an episode of OHE. All CLDQ domains were significantly poorer in patients with a breakthrough episode of OHE compared with patients remaining in remission [54].

Influence of other factors on HRQOL

Other clinical factors which have been shown to impact HRQOL include the presence of comorbidities, with one study of HCV patients showing increasing impairment of health utilities and SF-36 summary scores with increasing levels of comorbidity, as measured by either the Charlson score or the index of coexistent disease [55]. The number of different medications taken daily, which reflects the comorbidity burden, has also been demonstrated to be significantly associated with most domains of SF-36 and NHP [27]. Prescription of specific medications has also been studied; loop diuretics have been shown to be associated with impairment of most SF-36 domains [27], while in another study, diuretic and beta-blocker use were found to be the only two variables predictive of PCS in multivariate regression analysis, although their effects were limited to patients with decompensated cirrhosis [56]. A diagnosis of type 2 diabetes was associated with impaired MCS and PCS in a study of patients with NAFLD, while a BMI of >40 kg/m² affected the PCS [57]. In their study of patients with ascites, Sola et al. showed that hyponatraemia was an important contributor to impaired HRQOL with serum sodium identified as an independent predictive factor of both PCS and MCS in multivariate analysis [34]. The development of HCC has also been shown to adversely affect HRQOL. One study compared HCC patients to chronic liver disease controls, matched by age, sex, aetiology and disease severity, showing that HCC was associated with poorer HRQOL, affecting predominantly physical aspects of the NHP and SF-36 [58]. The need for detailed assessment of HRQOL in HCC has resulted in the development of HCC-specific measures as well as the use of generic cancer measures, which are reviewed elsewhere [59]. Interestingly, there is evidence that better HRQOL at baseline is associated with longer survival in HCC [60].

Non-clinical factors have also been considered with respect to HRQOL in advanced liver disease. One study which converted SF-36 and NHP to Z-scores compared with age- and sex-matched healthy controls showed that younger patients had greater impairment in HRQOL, most likely due to better HRQOL scores in younger controls relative to older controls [27]. Conversely, one study of 713 patients with NAFLD found that increasing age was significantly associated with poorer PCS, but not MCS, in univariate and multivariate analysis, however only 9.3% of this cohort were cirrhotic [57]. A correlation between increasing age and worsening SF-36 scores has been reported in another study of 1103 chronic liver disease patients (69% cirrhosis) [26]. These two studies also found in multivariate regression analysis that female patients had significantly poorer MCS and PCS scores [26,57]. Two studies showed that liver patients with lower income have significantly impaired PCS and MCS [55,57], while another showed an effect on two domains (Physical Functioning and Mental Health) [61]. In addition, this study showed that higher education level was associated with better mental health scores, while another showed NAFLD patients who did not attain a high school diploma had significantly poorer MCS than those who were better educated [57]. Patients who are married or living with a partner have been shown to have better HRQOL than those who are divorced, separated or widowed [55,57,62].

Conclusions

It is clear that advanced chronic liver disease is associated with dramatically impaired HRQOL. The literature provides key evidence to support a multifactorial model of HRQOL impairment in advanced liver disease. For example, we know that some of the clinical factors, which worsen HRQOL, include disease severity, the presence of ascites or encephalopathy and hyponatraemia. It is therefore unlikely that a single global intervention will improve HRQOL in advanced liver disease, but rather by systematically focusing on the individual contributing factors with a reversal component, overall improvements may be possible. Indeed there is some evidence to support improved HRQOL through effective treatment and improvement or resolution of decompensation. There is a significant need, however, to explore the responsiveness of HRQOL to systematic intervention to improve reversible manifestations of advanced liver disease such as ascites and encephalopathy in properly designed longitudinal studies using appropriate HRQOL outcome measures.

Modern healthcare places a great importance on demonstrating cost-effectiveness of new treatments. The methodology used in such technology appraisals is critically important as it affects whether or not a new treatment will be made available to patients, as exemplified by recent assessments of sorafenib for HCC [63]. QALYs vary greatly depending on the technique used for the derivation of health utility scores, as demonstrated with chronic HCV [64]. Many advocate the use of patient-derived utility scores, for which a robust measure of HRQOL is essential. There is also a drive to provide care, which is more patient-centric, with a focus on the issues which matter most to patients and their carers; hence, a greater emphasis on HRQOL in both clinical practice and research, is required.

Many treatments for advanced liver disease aim to be life-enhancing, rather than life-prolonging. Evaluation of future therapies should therefore include HRQOL assessment, with tools chosen to provide sensitivity to changes relevant to the clinical setting. We recommend the use of a robust generic measure, such as SF-36 or SIP, in combination with a disease specific measure. While there are more studies published using the CLDQ, serious consideration should be given to the use of the LDQOL, or the short-form version SF-LDQOL, as an alternative liver disease-specific measure in studies of cirrhosis, as these seem to provide greater responsiveness to changes seen in more advanced disease. Finally, consideration should be given to the way in which care delivery contributes; HRQOL driven service evaluation and improvement will likely bring further gains.

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Conflicts of interest

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Authors' contributions

J.G.O. reviewed the literature and wrote the manuscript, T.H., L.T., J.N., C.J.M., M.H., and D.E.J.J. reviewed the manuscript.

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