Quality of life and unmet needs in patients with chronic liver disease: A mixed-method systematic review

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Graphical abstract

How can we improve our patients’ quality of life?

- Better education and information
- Psychosocial support
- Public destigmatization

>37,000 patients say we need to focus on

Mixed method systematic review of 95 studies from 26 countries

Highlights
- Patients with liver disease regardless of aetiology and severity have impaired quality of life.
- Patients call for better education and information to understand and manage their liver disease, and for increased awareness and support from healthcare professionals.
- Owing to the limited knowledge of liver diseases among the general population, patients experience stigmatisation, resulting in loneliness and social isolation.
- Addressing unmet needs of patients with liver disease could improve their quality of life.

Lay summary
Regardless of aetiology, patients with liver diseases have impaired quality of life. This is associated with disease progression, the presence of symptoms, treatment response, and mental, physical, and social factors such as anxiety, confusion, comorbidities, and fatigue, as well as limitations in daily living, including loneliness, low income, stigmatisation, and treatment costs. Patients highlighted the need for information to understand and manage liver disease, and awareness and support from healthcare professionals to better cope with the disease. In addition, there is a need to raise awareness of liver diseases in the general population to reduce negative preconceptions and stigmatisation.

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Introduction
Chronic liver disease is commonly caused by alcohol abuse, non-alcoholic steatohepatitis (NASH), viral hepatitis, and autoimmune and may progress to cirrhosis. Liver disease is often associated with serious health problems, hospitalisations, and increased mortality.1 Although clinical management is important for the disease course and physical symptoms, there is usually a lack of focus on the patients’ experience of the disease and quality of life, both of which are important components when assessing the overall health status of patients and planning liver care.2 An important hindrance is the lack of knowledge of liver patients’ mental and social symptoms. These are often left unspoken and go unnoticed.3 This is an unsatisfactory situation because liver disease often negatively impacts patients’ family and social life, employment and financial status, and maintenance of health insurance, all sequelae that are often unseen by healthcare professionals.4

Therefore, the aim was to develop a convergent, integrated synthesis of quantitative and qualitative studies on the perceived quality of life in patients with chronic liver disease in an attempt to reveal unmet patient needs.

Patients and methods
This systematic review was conducted according to the Joanna Briggs Institute (JBI) methodology for mixed-method systematic reviews5 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.6 A protocol was developed to outline the objective, search strategy, selection criteria, data extraction method, and data synthesis methods.7 The review was registered in PROSPERO CRD42020173501.

Search strategy
A three-step search strategy was utilised.8 First, PubMed was searched with the search terms ‘quality of life’ and ‘liver disease’,...
followed by an analysis of the words contained in the titles and abstracts of relevant articles, and of the index terms used to describe the articles. Second, all three databases [CINAHL (via EBSCO), Embase (via Ovid), and PubMed (via Ovid)] were searched using all identified keywords and index terms from the first step from January 2000 to October 2020. To refine the depth and width of the search and to capture available relevant articles, Boolean operators (OR and AND) were utilised to combine keyword and index terms such as patients with ‘autoimmune liver disease’ or ‘cirrhosis’ and outcomes such as ‘patient experience’ or ‘quality of life’. Third, the reference list of all articles selected for critical appraisal and possible inclusion was manually searched for additional studies. Articles published in English were included. The search strategy is presented in Table S1. The search strategy was established in collaboration with a librarian from the hospital’s medical library.

**Study selection**

**Types of studies**
Quantitative data from observational analytical or descriptive studies (e.g. case-control studies, cross-sectional studies, and prospective and retrospective cohort studies) and qualitative studies regardless of design and method were included.

**Types of participants**
Studies that included patients with autoimmune and cholestatic liver disease, chronic hepatitis B and C, non-alcoholic fatty liver disease (NAFLD) and NASH, cirrhosis of different aetiologies, and hepatocellular carcinoma (HCC) were included. There was no restriction regarding disease severity, patient age, sex, or ethnicity. Studies on the experiences and quality of life of families with patients with liver disease or healthcare professionals were not included.

**Phenomena of interest**
Studies with the primary aim of exploring the quality of life of patients with liver disease using either generic or liver-specific questionnaires were included. Studies comparing patients with liver disease to control groups or general population norms and studies comparing patients with different types of liver diseases or patients with liver disease to other patients with chronic disease were included. Studies exploring patients’ changes in quality of life after clinical interventions were excluded. Finally, studies exploring the experiences and quality of life of patients awaiting or receiving a liver transplant were not included in the review. Qualitative studies that described patients’ experience and perception of having a liver disease were included.

**Article screening**
Following the search, the articles were imported into a reference management program (Endnote X9, Clarivate Analytics, PA, USA), and duplicate citations were removed. Thereafter, the titles and abstracts of the articles identified from the searches were screened and selected articles were individually reviewed. The full text of the articles selected was obtained and assessed for eligibility. Reasons for excluding any full-text articles were recorded and are presented in Table S2.

**Assessment of methodological quality**
The studies were critically appraised using the standardised critical appraisal instrument for quantitative and qualitative studies from JBI SUMARI presented in Table S3. All studies were included in the review regardless of methodological quality. At any step of the method phase, any disagreements were resolved through a discussion between the authors or input from a research colleague until a consensus was reached.

**Data extraction**
Quantitative and qualitative data were extracted from the included articles using the standardised JBI data extraction instrument JBI SUMARI. These data included details on the authors, year of publications, study methodologies, patient populations and characteristics, including sample sizes, data collection methods, and outcomes of significance to the review objective. If possible, factors demonstrating a significant association with quality of life were extracted. A table of the data extraction is presented in Table S4.

**Data synthesis**
A descriptive assessment of the data based on the extracted outcomes, followed by a convergent integrated approach according to the JBI methodology for mixed-method systematic reviews, was performed. This involved quantitative data being presented as textual descriptions and assembled with qualitative data. The assembled data were categorised based on the similarity in their meanings in an attempt to reveal unmet patient needs and to suggest directions to meet these needs and improve quality of life.

**Results**
The searches produced a total of 5,601 articles. After the elimination of duplicates, 3,144 articles were reviewed based on titles and abstracts, and 115 were identified for full-text assessment. After full-text reviews, 95 articles (79 quantitative and 16 qualitative) met the inclusion criteria. A summary of the process is presented in the flowchart in Fig. 1.

**Description of included articles**
The included articles represented studies from 26 different countries across 6 continents, with the majority being from Asia (36%), Europe (32%), and North America (30%). Among the 79 quantitative studies, the majority were cross-sectional (76%). Studies had a patient population size from 15 to 7,098, and 52% of the studies used control groups or general population norms for comparison. Seventy percent of the studies used generic questionnaires on quality of life, with different versions of the Short Form (SF) being the most common (51%), whereas 47% of the studies used liver-specific questionnaires with the Chronic Liver Disease Questionnaire (CLDQ) being the most common (30%). All 16 qualitative studies used interviews as a data collection method. The most common analysis method was content analysis (38%), followed by phenomenological (31%) and thematic analysis (19%). The patient population size was between 8 and 41 patients.

**Methodological quality of the included studies**
A majority of the studies (92%) were categorised as having good or moderate methodological quality. The mean quality score of the quantitative studies was 7.1 (range 4–9), and the mean score for the qualitative studies was 8.2 (range 7–10). The most common source of bias was a lack of description of the patient...
population or control group, general characteristics, sampling method, and inadequate descriptions of statistical analysis and results.

**Description of included patients**

The patient population consisted of patients with autoimmune or cholestatic liver disease (19 studies), chronic hepatitis B or C (35 studies), NAFLD or NASH (15 studies), cirrhosis of different aetiologies (but mainly alcohol and hepatitis; 17 studies), and HCC (9 studies). Six studies explored the quality of life in children with liver disease (3 in children with autoimmune or cholestatic liver disease, 2 in children with NAFLD and 1 in children with hepatitis B). A total of 37,283 patients participated in the included studies. Half of the studies included patients aged 50 years or older. Most studies on patients with chronic hepatitis B or C included patients under 50 years of age (71%). Fifty-five percent of the studies had a patient population with more men than women. However, in studies of patients with autoimmune or cholestatic disease, more women than men were included (83%). In all of the included studies, most of the patients were Child-Pugh class A (64%) and had a model for end-stage liver disease (MELD) score under 15 (56%). Most studies (89%) included patients from various gastroenterology and hepatology in- and outpatient settings, whereas the rest used data from national surveys or from patient-reported outcome databases. The characteristics of the studies and the patients are presented in Table 1.

**Patients' quality of life**

Patients' quality of life was reduced compared with control groups or the general population, regardless of the liver disease aetiology. The use of questionnaires and the presentation of...
Table 1. Characteristics of studies and patients (N = 95).

| Study design and method | Number of studies (%) |
|-------------------------|-----------------------|
| Quantitative studies (all using questionnaire) | 79 (83%) |
| Cross-sectional study | 60 (76%) |
| Prospective study | 14 (18%) |
| Case-control study | 5 (6%) |
| Qualitative studies (all using interview) | 16 (17%) |
| Content analysis | 6 (36%) |
| Phenomenological analysis | 5 (31%) |
| Thematic analysis | 3 (19%) |
| Grounded theory analysis | 1 (6%) |
| Combination of analyses | 1 (6%) |

Study design divided into liver disease group

| Liver disease | Quantitative studies (%) | Qualitative studies (%) |
|---------------|--------------------------|-------------------------|
| Autoimmune or cholestatic liver disease | 17 (18%) | 2 (2%) |
| Hepatitis B or C | 28 (29%) | 7 (7%) |
| NAFLD and/or NASH | 13 (14%) | 2 (2%) |
| Cirrhosis of different aetiologies | 14 (15%) | 3 (4%) |
| Hepatocellular carcinoma | 7 (7%) | 2 (2%) |

Quality of life questionnaire

| Questionnaire | Genuin questionnaire | Short Form (SF-6D, SF-8, SF-12, SF-36) | European Quality of Life (EQ-5D) | Pediatric Quality of Life Inventory (PedsQL) | Other |
|---------------|---------------------|----------------------------------------|---------------------------------|--------------------------------|-------|
| | 59 (70%) | 40 (51%) | 10 (13%) | 5 (6%) | 4 (5%) |
| Liver-specific questionnaires | 37 (47%) | 24 (30%) | 5 (6%) | 4 (5%) | 20 (25%) |
| Chronic Liver Disease Questionnaire (CLDQ) | 24 (30%) | 10 (13%) | 3 (3%) | 3 (3%) | 1 (1%) |
| Primary Biliary Cholangitis Questionnaire (PBC) | 3 (3%) | 2 (2%) | 1 (1%) | 1 (1%) | 1 (1%) |
| Functional Assessment of Cancer Therapy Hepatobiliary carcinoma (FACT-Hep) | 3 (3%) | 2 (2%) | 1 (1%) | 1 (1%) | 1 (1%) |
| Other | 4 (5%) | 2 (2%) | 1 (1%) | 1 (1%) | 1 (1%) |

Age group (Reported in 81 studies)

- <50 years: 37 (46%)
- 50–60 years: 33 (41%)
- >60 years: 11 (13%)

Sex (Reported in 88 studies)

- <50 men: 36 (41%)
- 50–60 men: 18 (20%)
- >60 men: 34 (39%)

Disease severity (Reported in 11 and 9 studies)

- Child-Pugh class A > 50%: 7 (64%)
- Child-Pugh class B or C > 50%: 4 (36%)
- Model of end-stage liver disease (MELD) score <15: 5 (56%)

Table 1 (continued)

| Study design and method | Number of studies (%) |
|-------------------------|-----------------------|
| Patients with NAFLD and/or NASH | 7,246 (19%) |
| Patients with cirrhosis of different aetiologies were associated with impaired quality of life.79,81,83 | 2,696 (8%) |
| Patients with hepatocellular carcinoma | 1,254 (3%) |

- Age group (Reported in 81 studies)
  - <50 years: 37 (46%)
  - 50–60 years: 33 (41%)
  - >60 years: 11 (13%)

- Sex (Reported in 88 studies)
  - <50 men: 36 (41%)
  - 50–60 men: 18 (20%)
  - >60 men: 34 (39%)

- Disease severity (Reported in 11 and 9 studies)
  - Child-Pugh class A > 50%: 7 (64%)
  - Child-Pugh class B or C > 50%: 4 (36%)
  - Model of end-stage liver disease (MELD) score <15: 5 (56%)

Patients’ experience of having a liver disease

Patients had fear of the disease outcome, their physical condition, and treatment costs. They were shocked to be diagnosed with a liver disease, which triggered a life transition.29,37,55,80,88 Although patients with hepatitis B also understood the disease as an intergenerational family condition.29 Patients generally tried to manage the disease in a positive way, but a lack of knowledge could result in insufficient self-care. This resulted in a feeling of failure.29,37,35,80,88

Across aetiologies, patients described being afraid to reveal having liver disease because of the fear of misperception. Patients adopted a number of strategies such as denial to protect themselves. The diagnosis of liver disease introduced a feeling of stigmatisation in all patient groups caused by attributes associated with the disease such as alcohol or drug use. This resulted in social distance and isolation, which negatively impacted patients’ social life.29,37,55,80,88

Patients with autoimmune and cholestatic liver disease described that having an invisible and rare disease resulted in quality of life scores varied, which made comparison across aetiology and severity of the liver disease difficult. See Table 2 for summary of findings from the included studies. Disease progression was found to be associated with impaired quality of life.79,81,83

Other disease-related factors such as disease duration and severity, response to treatment, and side effects of medication also negatively affect the quality of life in patients.3,12,22–26

Mental, physical, and social factors, such as body composition, comorbidities, fatigue, lack of information on the disease, and low income together with patient characteristics, such as younger age at diagnosis, alcohol use, and female sex, were associated with impaired quality of life.6,10,13,15,18,21,30,33,35,42

Patients with cirrhosis felt more limitations in their daily living because of disease progression and symptoms than patients with less severe liver diseases, which resulted in a feeling of loss of self and loneliness.29,37,55,80,88

Patients with cirrhosis felt vulnerable when experiencing symptoms and had difficulties
with treatment compliance. Some patients expressed being religious or spiritual, which gave them a sense of faith and hope. Patients with HCC were highly aware of changes and new symptoms. They described a desire to control how the disease was affecting their quality of life, which navigated treatment decisions.

Patients' unmet needs
Regardless of liver disease aetiology, all patients described that limited information and understanding of the disease created anxiety and considerable confusion. Patients expressed a need for awareness and support from healthcare professionals to cope with liver disease. In particular, patients with NAFLD or NASH admitted poor understanding of the disease. Some patients were advised to make lifestyle modifications but did not receive any information or support on how to proceed. Others were told that NAFLD should not be a concern and that comorbidities were of greater concern.

Table 2. Summary of findings from studies included in the systematic review.

| Patients | Autoimmune or cholestatic liver disease | Chronic hepatitis B or C | NAFLD or NASH | Cirrhosis | HCC |
|----------|----------------------------------------|--------------------------|---------------|-----------|-----|
| **Quantitative studies** | **Quality of life total mean scores of patients with liver diseases across the included studies** | **Quality of life total mean scores of patients with liver diseases across the included studies** | **Quality of life total mean scores of patients with liver diseases across the included studies** | **Quality of life total mean scores of patients with liver diseases across the included studies** | **Quality of life total mean scores of patients with liver diseases across the included studies** |
| **Chronic Liver Disease Questionnaire (CLDQ) mean score** | 5.5** | 4.1–5.8 | 4.9–5.6† | 4.3–5.3‡ | – |
| **European Quality of Life (EQ-SD) mean score** | 0.89** | 0.37–1.0† | 0.67** | – | – |
| **Hepatitis B Quality of Life (HBQOL) mean score** | – | 64.4–81.4‡ | – | – | – |
| **Short-Form (SF) different versions** | 40.1–66.7* | 43.0–51.3* | 39.2–49.5* | 41.0–45.3‡ | – |
| **Functional Assessment of Cancer Therapy-Hepatobiliary Carcinoma (FACT-Hep) mean score** | – | – | – | 189** | – |
| **Liver Cirrhosis Patient Reported Outcome Measure (LC-PROM) mean score** | – | – | – | 55.3** | – |
| **Pediatric Quality of Life Inventory (PedsQL) mean score** | 71.6–78.3 | 72.7–74.58* | – | – | – |
| **Primary Biliary Cholangitis Questionnaire (PBC) mean score** | 89.4** | – | – | – | – |
| **Sickness Impact Profile (SIP) mean score** | – | – | – | 4.36** | – |
| **WHO Quality of Life (WHOQOL-BREF) mean score** | 6 (35%) | 2 (15%) | 3 (21%) | 2 (28%) | – |
| **Studies reporting quality of life results in graphic, number and %** | 3 (18%) | 3 (21%) | 0 (0%) | 2 (14%) | 1 (14%) |

Range of quality of life scores indicate minimum and maximum total mean score from studies using the questionnaire. HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

* Indicates the use of the questionnaire in 5–9 studies.
† Indicates the use of the questionnaire in 4 studies.
‡ Indicates the use of the questionnaire in 2 studies.
** Indicates the use of the questionnaire in 1 study.
tion, patients experienced negative preconceptions and stigmatisation because of sparse knowledge of liver disease in the general population. Based on the findings, a conceptual model of the impact of liver disease on patients’ quality of life was developed (Fig. 2).

**Discussion**

This systematic review sought to explore patients’ quality of life and their experience of having a chronic liver disease and to reveal unmet needs. We found that regardless of aetiology, the quality of life was impaired in patients with liver disease as a result of disease progression and several mental, physical, and social factors. Patients highlighted an unmet need for information to understand and manage their liver disease and awareness and support from healthcare professionals to better cope with their situation. In addition, negative preconceptions and stigmatisation negatively affected patients’ quality of life.

This is the first systematic review on the quality of life in patients with liver disease that uses a mixed-method approach. Mixed-method research originated in social science, but has recently expanded into health science. It integrates quantitative measures with qualitative analyses, which helps provide a wider and deeper understanding of the impacts of liver diseases on patients’ quality of life. The strength of this review is the systematic approach. The development of a search protocol before the review helped to reduce the impact of biases, ensure accountability and transparency, and maximise the likelihood of correct data extraction. The weaknesses of the review are the possibility that relevant articles were not included because of language limitations and the fact that only a limited number of databases were searched. In addition, the review does not include grey literature and may thus be subject to publication bias. The quality of the review depends on the quality of the studies included. Most studies, whether quantitative or qualitative, had moderate or good methodological quality. A common source of bias was the lack of descriptions of patients’ demographics; therefore, it is possible that the patients studied were not necessarily representative of the entire population of patients with liver disease. In addition, most studies were cross-sectional in design, so causal inference cannot be drawn from the results. Moreover, studies used in the review examined a wide range of factors associated with quality of life without a priori hypotheses; therefore, the findings might be incidental. However, given the extensive nature of this review, this error would be minimised by repeated findings in several studies, increasing the confidence in the external validity of the observed associations.

The review was successful in identifying studies from 26 different countries across 6 continents. Although our findings on patients’ quality of life are consistent across different countries,
only a few studies from Africa and South America, areas where liver disease is a major health burden, were identified.\textsuperscript{105}

Regardless of the aetiology of the liver disease, patients’ quality of life was impaired. The pattern of impairment may vary between different aetiologies and severity. However, the heterogeneous nature of the different questionnaires used to measure quality of life and the ways in which findings were reported made comparison challenging. This has been highlighted in other studies, which recommend the use of a robust generic questionnaire in combination with a disease-specific questionnaire to measure quality of life in patients with liver disease. In addition, it has been suggested that further studies on quality of life should incorporate a qualitative element, which would be valuable in determining the full humanistic burden of living with a liver disease.\textsuperscript{106}

Our review identified an unmet need for patient information. Limited knowledge has been identified as a significant barrier to disease management.\textsuperscript{107} One practical implication is to provide written information to address patients’ information needs concerning liver disease and treatment. Such a simple educational intervention has proven to increase the patients’ knowledge.\textsuperscript{108} However, it remains to be seen whether increased patient knowledge will translate into improved quality of life. In addition, an emerging area of research in the field of improving patient knowledge is health literacy, that is, the capacity to have limited health literacy.\textsuperscript{109} Therefore, larger intervention studies are needed to determine which educational efforts are valuable in determining the full humanistic burden of living with a liver disease.\textsuperscript{106}

In conclusion, this is the first mixed-method systematic review that summarises findings from a growing body of literature on the quality of life of patients with liver disease. Our review substantiates the general conception that, regardless of aetiology, liver disease has major impact on patients’ lives. As something new, our methodology makes way for a deeper understanding by exploring the main self-reported causes of impaired quality of life. Apart from the symptoms of liver disease, these causes include unmet needs for information, education, and their impact on patients’ quality of life.

In conclusion, this is the first mixed-method systematic review that summarises findings from a growing body of literature on the quality of life of patients with liver disease. Our review substantiates the general conception that, regardless of aetiology, liver disease has major impact on patients’ lives. As something new, our methodology makes way for a deeper understanding by exploring the main self-reported causes of impaired quality of life. Apart from the symptoms of liver disease, these causes include unmet needs for information, education, support from families and healthcare professionals, and their impact on patients’ quality of life.

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Supplementary data

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Abbreviations

CLDQ, Chronic Liver Disease Questionnaire; EQ-5D, European Quality of Life; FACT-Hep, Functional Assessment of Cancer Therapy Hepatobiliary Carcinoma; HBQOL, Hepatitis B Quality of Life; HCC, hepatocellular carcinoma; JBI, Joanna Briggs Institute; LC-PROM, Liver Cirrhosis Patient Reported Outcome Measure; LDQOL, Liver Disease Quality of Life; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PBC, Primary Biliary Cholangitis Questionnaire; PedsQL, Pediatric Quality of Life Inventory; SF, Short Form; SIP, Sickness Impact Profile; VAS, visual analogue scale; WHOQOL-BREF, WHO Quality of Life.

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Conflicts of interest

The authors do not have any conflicts of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors’ contributions

Contributed to the study concept and design: L.L.G. Contributed to the data collection, analysis, writing, and conceptualisation of the manuscript: both authors.

Data availability statement

The dataset used in this study is available from the corresponding author on reasonable request.
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