

# Improving Health-Related Quality of Life in Hepatocellular Carcinoma Patients: Key Methodologies for Assessing Patient Reported Outcomes and Intervention Targets

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**Abstract:** Hepatocellular carcinoma (HCC) is a complex cancer that generally arises in the context of cirrhosis. Patients with HCC have symptom burden and impact on health-related quality of life (HRQOL) resulting from underlying liver disease, HCC, and cancer treatments. Patient-reported outcome (PRO) measures may improve the management of patients with HCC by accurately capturing the patient perspective, informing prognosis, guiding treatment decisions, and supporting symptom based and palliative care. Furthermore, PRO use in HCC research could enhance patient-focused therapy development. This review focuses on the clinical and research assessment of PROs among patients with HCC.

**Keywords:** liver cancer, cirrhosis, PROs, HRQOL

## Introduction

Hepatocellular carcinoma (HCC) is a uniquely complex cancer that typically arises in the context of chronic liver disease and cirrhosis.<sup>1,2</sup> Managing HCC and assessing clinical outcomes in these patients can be challenging. Symptoms such as fatigue, gastrointestinal problems and weight loss may be attributable to chronic liver disease, HCC tumor burden, or treatment-related side effects.<sup>3</sup> These multiple contributors to symptom burden can complicate patient management given that HCC treatments may improve cancer-specific symptoms but exacerbate treatment-related side effects and worsening of liver function, leading to ascites, hepatic encephalopathy, and variceal bleeding.<sup>4-8</sup> Furthermore, there are several treatment options for HCC offered by different medical, radiological, or surgical subspecialties.<sup>9</sup> Treatment decisions are best made in the context of multidisciplinary discussions in which tradeoffs among benefits, risks, inconvenience, costs, and patient preferences are considered.<sup>9</sup> However, many patients face barriers to accessing multidisciplinary care and co-located HCC clinics with multiple specialists on staff are unavailable at most centers.<sup>9-11</sup> Lastly, HCC has traditionally had a poor prognosis and high symptom burden, which leads to impaired health-related quality of life (HRQOL) as well as substantial caregiver burden.<sup>12,13</sup> The complexity of HCC- and treatment-related symptoms requires accurate and reliable assessment of symptom burden, HRQOL, and mental health to improve health and treatment outcomes for these patients.

Patient-reported outcomes (PROs) are reports on the status of a patient's health elicited directly from the patient without interpretation by the clinician or anyone else.<sup>14</sup> PROs have been shown to provide more accurate information about symptom burden compared to provider report. Compared to clinicians, patients with cancer report symptoms earlier, with greater

frequency, and at higher intensity suggesting that clinicians underestimate symptom burden.<sup>15–17</sup> Discrepancies are particularly common for more subjective symptoms such as fatigue and confusion, commonly encountered in patients with HCC.<sup>3,18</sup> The feasibility of collecting PROs has been demonstrated in research settings and the US Food and Drug Administration (FDA) has encouraged using PRO measures to evaluate patient-centered outcomes of interest in therapeutic trials.<sup>3,14,19</sup> However, in the clinical setting, administrative requirements and costs are potential barriers to their adoption.<sup>20</sup> Progress has been made, however, to encourage PRO collection in routine clinical care, such as alternative payment models that require the incorporation of PROs.<sup>21,22</sup> Research and early clinical experiences suggest that PRO measures enhance care.<sup>3</sup> Specifically in HCC, the use of PRO measures has improved care by capturing patient perspectives, guiding treatment decisions, informing prognosis, enhancing patient-focused drug development, and supporting symptom-based and palliative care.<sup>3</sup>

This review will focus on the assessment of PRO measures and how to incorporate PROs into caring for the patient with HCC, informing treatment decision-making, and conducting patient-centered research. Currently, PRO measures are primarily used as outcomes in HCC-related research but have potential future promise in guiding treatment decisions in clinical practice. This review is meant to inform clinicians and researchers of the best evidence regarding the assessment and improvement of these outcomes among patients with HCC.

## Approach to Developing and Assessing PRO Measures

There are multiple qualitative and quantitative steps involved with the development and validation of PRO measures.<sup>23</sup> First, key concepts of interest relevant to the target population need to be elicited (eg, symptoms, aspects of HRQOL and functioning) through literature searches and qualitative work with patients, researchers, and clinicians. Data from this step is used to develop conceptual and measurement models.<sup>24</sup> Survey design experts then construct a draft PRO questionnaire inclusive of instructions, items, recall period and response options. The questionnaire must then undergo multiple rounds of cognitive interviewing to assess clarity, acceptability, and relevance. The instrument must then undergo quantitative evaluation of its internal properties and external validity including association with PRO measures of similar concepts.<sup>25</sup> The process of validation involves several different aspects that assess whether the instrument functions effectively for a given set of patients in a specific setting (eg, outpatient, inpatient).

The responsiveness of a PRO instrument refers to its ability to detect changes in response to treatments or patients' health status over time.<sup>23</sup> Specifically, a responsive measure should worsen if a patient's HCC or liver disease progresses and remain stable if a patient has had no change in health status. For example, studies have assessed the responsiveness of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-HCC18 disease-specific measure by quantifying changes in scores before and after surgery, ablation, and transarterial embolization.<sup>26–28</sup> Studies have demonstrated significant worsening of pain and fatigue after treatment, supporting this instrument's responsiveness to change.

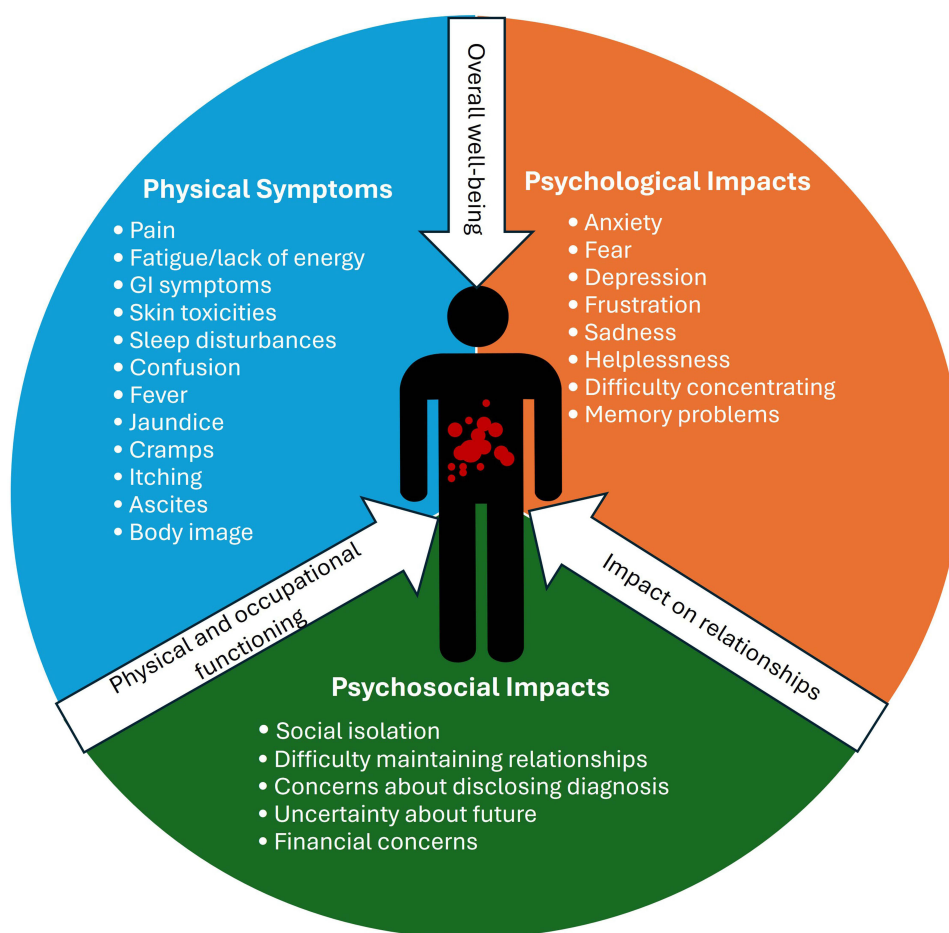
One important aspect of responsiveness is the distinction between statistically significant and clinically significant changes.<sup>29</sup> Clinically significant differences are improvements in HRQOL or its components (eg, functional improvements) that would be considered sufficiently consequential to a patient such that they would undergo the same intervention if offered the opportunity.<sup>30,31</sup> The minimal clinically important difference (MCID) is a concept of clinically significant differences defined by Jaeschke et al as the smallest difference which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management.<sup>31</sup>

Of note, the FDA has defined what constitutes meaningful score differences (MSD) and endorsed the use of within-cohort anchor-based methodology for assessing clinically significant differences.<sup>32</sup> The FDA guidance notes that individual patients likely differ in what may be considered an MSD and, when interpreting clinical trial results, a range of MSD should be used that reflects most patients.

## PRO Instruments for HCC

When considering PRO instruments for HCC, it is important to understand the common symptoms experienced by patients with HCC. There are several physical, psychological, and psychosocial factors that are impacted by HCC (Figure 1) that should be considered when selecting PRO instruments for research or clinical use.<sup>3,8</sup>

There are several generic, cancer-specific, and liver cancer-specific PRO instruments that have been used in studies of patients with HCC (Table 1). When selecting between specific measures, it is important to consider the goal of the PRO



**Figure 1** The impact of HCC and its treatments on patient well-being.

instruments (eg, clinical care or research), the setting (eg, remote monitoring vs in clinic), clinical characteristics of patients (eg, disease stage, treatment types, degree of liver dysfunction), and other factors including sociodemographics, culture, language, and literacy.<sup>14,51–53</sup> Lastly, researchers and clinicians should consider practical aspects including the mode of survey administration (eg, self-administered, interviewer administered, paper vs electronic) and the availability and validation of instruments in various languages and across cultures.

There are clear tradeoffs between generic and disease-specific instruments.<sup>53,54</sup> Generic instruments capture a wide range of HRQOL aspects that are relevant to the general population and multiple health conditions and therefore provide a holistic, multidimensional view of patients' well-being. Utilizing generic instruments may allow for comparisons between patients with HCC and other cancer or chronic disease populations to provide insights into the relative burdens of HCC. Many generic instruments have undergone extensive validation and are widely accepted for measurement of HRQOL. However, generic instruments may be less sensitive to small changes in HRQOL when compared to measures more specific to HCC and cirrhosis. Additionally, generic instruments may not include symptoms or complications commonly experienced by patients with HCC, including liver-related decompensation events (eg, ascites or cognitive dysfunction).<sup>3</sup> Disease-specific PRO instruments, in contrast, allow for more targeted and sensitive assessments of HCC-specific symptoms at the expense of more limited comparability and less prior validation of instruments. While there are no PRO instruments that have undergone all steps of qualitative development and psychometric evaluation among patients with HCC, both the EORTC and Functional Assessment of Cancer Therapy (FACT) measures (eg, QLQ-HCC18, FACT-Hepatobiliary; FACT-Hep) were developed in populations that included some HCC patients and have been extensively used for HCC trials (Table 1).<sup>3</sup>

**Table 1** HRQOL Instruments That Have Been Used in Research of Patients with HCC

Instrument Type	Instrument Name	Author/Citation	Description	Pros/Cons of PRO Instrument
Generic	Short Form (SF)-36	Ware <sup>33</sup>	Generic HRQOL instrument measuring eight health domains, including physical functioning, role limitations, bodily pain, general health, vitality, social functioning, emotional well-being, and mental health	Pros: <ul style="list-style-type: none"> <li>● Widely used</li> <li>● Well-validated</li> <li>● Good for comparing to general population</li> </ul> Cons: <ul style="list-style-type: none"> <li>● Not specific for liver disease or cancer</li> <li>● Less sensitive for HCC-specific issues</li> <li>● Less focus on symptoms</li> </ul>
	Short Form (SF)-12	Ware <sup>34</sup>	Shorter version of the SF-36, assessing the same eight health domains with fewer questions	Similar Pros/Cons to SF-36 Less comprehensive than SF-36 but more practical due to shorter length
	EQ-5D	EuroQol Group <sup>35</sup>	Generic instrument that measures five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.	Pros: <ul style="list-style-type: none"> <li>● Brevity</li> <li>● Provides a utility score for quality-adjusted life year scores</li> <li>● Can be used across a wide range of diseases</li> </ul> Cons: <ul style="list-style-type: none"> <li>● Limited scope</li> <li>● Not disease-specific</li> <li>● Less sensitive and responsive to HCC-related concerns</li> </ul>
	World Health Organization Quality of Life (WHOQOL)-100	WHOQOL Group <sup>36</sup>	Comprehensive instrument developed by the World Health Organization, measuring various aspects of HRQOL across six domains: physical health, psychological health, level of independence, social relationships, environment, and spirituality/religion/personal beliefs	Pros: <ul style="list-style-type: none"> <li>● Comprehensive with multiple domains</li> <li>● Well-established tool for measuring HRQOL</li> <li>● Available in more than 40 languages allowing for cross-cultural comparisons</li> </ul> Cons: <ul style="list-style-type: none"> <li>● Lengthy (100 items)</li> <li>● Difficult to administer and interpret</li> <li>● Not disease specific</li> </ul>
	World Health Organization Quality of Life (WHOQOL)-BREF	WHOQOL Group <sup>37</sup>	Shorter version of the WHOQOL-100, covering the same six domains with fewer questions	Similar Pros/Cons to WHOQOL-100 Less comprehensive but more practical than WHOQOL-100

Spitzer Quality of Life Index (SQLI)	Spitzer <sup>38</sup>	Brief instrument measuring a patient's overall perception of their quality of life across five domains: activity, daily living, health, support, and outlook	<p>Pros:</p> <ul style="list-style-type: none"> <li>● Short and easy to administer</li> <li>● Designed to be used by physicians for clinical assessments and decision-making</li> <li>● Good inter-rater reliability</li> </ul> <p>Cons:</p> <ul style="list-style-type: none"> <li>● Limited scope and scoring range</li> <li>● May not capture the full spectrum of the patient's experience</li> <li>● Not patient-reported</li> </ul>
Patient-Reported Outcomes Measurement Information System (PROMIS)-29	Hays <sup>39</sup>	Collection of items from PROMIS item banks that measure health domains relevant to chronic diseases: physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, sleep disturbance	<p>Pros:</p> <ul style="list-style-type: none"> <li>● Efficient and highly usable</li> <li>● Comprehensive scope and depth</li> <li>● Standardized scoring</li> <li>● Customizable</li> </ul> <p>Cons:</p> <ul style="list-style-type: none"> <li>● General measure</li> <li>● Missing domains for patients with liver disease</li> <li>● Potential floor and ceiling effects</li> </ul>
Edmonton Symptom Assessment Scale (ESAS)	Watanabe <sup>40</sup>	Instrument used to assess common symptoms experienced in advance illness including pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath	<p>Pros:</p> <ul style="list-style-type: none"> <li>● Brevity and ease of use</li> <li>● Comprehensive assessment of symptoms</li> <li>● Validated in patients with cirrhosis</li> </ul> <p>Cons:</p> <ul style="list-style-type: none"> <li>● Not disease-specific</li> <li>● Does not capture all symptoms common in patients with liver disease or HCC</li> <li>● Less validation than other generic measures</li> </ul>

(Continued)

Table I (Continued).

Instrument Type	Instrument Name	Author/Citation	Description	Pros/Cons of PRO Instrument
Cancer-specific	European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30	Fayers <sup>41</sup>	Instrument assessing physical, role, emotional, cognitive, and social functioning, as well as symptoms like fatigue, nausea, and pain	Pros: <ul style="list-style-type: none"> <li>● Comprehensive assessment of generic- and cancer-specific issues</li> <li>● Widely used and validated</li> <li>● Simple scoring (0–100)</li> </ul> Cons: <ul style="list-style-type: none"> <li>● Unclear interpretation of clinical meaningfulness</li> <li>● Burden on patients</li> </ul>
	Functional Assessment of Cancer Therapy - General (FACT-G)	Cella <sup>42</sup>	Questionnaire focusing on physical, social, emotional, and functional well-being	Pros: <ul style="list-style-type: none"> <li>● Easy to administer and score</li> <li>● Good reliability and validity</li> <li>● Sensitive to clinical changes and well-established clinically meaningful differences</li> </ul> Cons: <ul style="list-style-type: none"> <li>● Limited coverage of social quality of life</li> <li>● Not comprehensive for all symptoms common in cirrhosis and HCC</li> </ul>
	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)	Basch <sup>43</sup>	Standardized measurement system designed to capture patient-reported symptomatic adverse events experienced during cancer treatment	Pros: <ul style="list-style-type: none"> <li>● Includes a comprehensive library of symptomatic adverse events and can be adapted to setting</li> <li>● Frequency, severity and interference of AEs can be assessed</li> <li>● Multiple administration modes</li> </ul> Cons: <ul style="list-style-type: none"> <li>● It can be difficult to choose which items to select</li> <li>● Focuses on symptoms but no other components of HRQOL</li> </ul>
	Brief Pain Inventory-Short Form	Cleeland <sup>44</sup>	Instrument to measure pain location, pain severity (worst, least, average, right now), improvement from pain medications and pain interference	Pros: <ul style="list-style-type: none"> <li>● Quick and easy completion</li> <li>● Clear use for assessing pain</li> </ul> Cons: <ul style="list-style-type: none"> <li>● Limited scope</li> <li>● May not capture complexity of pain</li> <li>● Not specific to HCC</li> </ul>
	MD Anderson Symptom Inventory (MDASI)	Cleeland <sup>45</sup>	Multi-symptom assessment tool that assesses several symptoms items and interference with physical activity, social activity, enjoyment of life and mood	Pros: <ul style="list-style-type: none"> <li>● Validated for measuring severity of symptoms in cancer patients</li> <li>● Good psychometric properties</li> </ul> Cons: <ul style="list-style-type: none"> <li>● Limited scope, particularly for HCC</li> <li>● Assesses the amount and severity of symptoms, but not symptom distress</li> </ul>

	Memorial Symptom Assessment Scale (MSAS)	Portenoy <sup>46</sup>	Assesses symptom frequency, severity and distress or bother of 32 symptoms	<p>Pros:</p> <ul style="list-style-type: none"> <li>Measures multiple dimensions of a wide range of symptoms</li> <li>Well established psychometric properties</li> <li>Takes 10–15 minutes to complete</li> </ul> <p>Cons:</p> <ul style="list-style-type: none"> <li>No global score due to multiple subscores</li> <li>No comparison to normative sample</li> <li>Not commonly used, particularly for HCC</li> </ul>
<b>HCC-Specific</b>	European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-HCC18	Blazeby <sup>47</sup>	Module designed to supplement the EORTC QLQ-C30, specifically addressing symptoms and concerns relevant to patients with HCC, including fatigue, body image, jaundice, nutrition, pain, fever, abdominal swelling, and sex life	<p>Pros:</p> <ul style="list-style-type: none"> <li>HCC-specific focused survey that complements EORTC QLQ-C30</li> <li>Patient-centered development in HCC</li> <li>Cross-cultural validity</li> </ul> <p>Cons:</p> <ul style="list-style-type: none"> <li>Associated with higher respondent burden</li> <li>Interpretation complicated by scoring system</li> </ul>
	Functional Assessment of Cancer Therapy - Hepatobiliary (FACT-Hep)	Heffernan <sup>48</sup>	45-item self-report module specifically designed for patients with hepatobiliary cancers that includes the FACT-G, assessing generic HRQOL, and the 18-item hepatobiliary subscale, that assesses disease-specific items	<p>Pros:</p> <ul style="list-style-type: none"> <li>Disease-specific and comprehensive</li> <li>Validated in patients with HCC</li> <li>Sensitive to changes in disease progression and treatment response</li> </ul> <p>Cons:</p> <ul style="list-style-type: none"> <li>High respondent burden</li> <li>May not capture psychological or spiritual aspects of HCC</li> </ul>
	FACT Hepatobiliary Symptom Index (FHSl-8)	Cella <sup>49</sup>	Abbreviated symptom index derived from the FACT-Hep, focusing on key symptoms of hepatobiliary cancers	<p>Pros:</p> <ul style="list-style-type: none"> <li>Brief and efficient assessment of key symptoms</li> <li>Designed for use in clinical trials and routine clinical practice</li> </ul> <p>Cons:</p> <ul style="list-style-type: none"> <li>Limited scope</li> <li>Loss of precision compared to FACT-Hep</li> </ul>
	National Comprehensive Cancer Network (NCCN)-Functional Assessment of Cancer Therapy–Hepatobiliary–Pancreatic Symptom Index (NFHSl-18)	Butt <sup>50</sup>	18-item scale that includes an assessment of symptoms, treatment-side effects, and general HRQOL specific to patients with advanced liver, bile duct and pancreas cancers	<p>Pros:</p> <ul style="list-style-type: none"> <li>Focused on symptoms experienced by patients with hepatobiliary and pancreatic cancers</li> <li>Multi-dimensional and with comprehensive symptom coverage</li> </ul> <p>Cons:</p> <ul style="list-style-type: none"> <li>More burdensome than other symptom measures (eg, FHSl-8)</li> <li>Does not capture social or emotional well-being</li> </ul>

Finally, the appropriate selection of a PRO measure may hinge on its floor and ceiling effects.<sup>23</sup> Floor and ceiling effects reflect the scales responsiveness at different extremes, based on the clustering of responses at the bottom or worst and top or best ends of the scale. A floor effect exists when a significant proportion of respondents have responses at the bottom end of the scale, limiting the responsiveness of a scale at its lower extremes. Conversely, a ceiling effect describes a high proportion of respondents selecting the best response option. A ceiling effect limits the ability of a scale to differentiate between those at the top end of the scale. The presence of strong floor or ceiling effects may influence the choice of PRO instrument. It may also be possible to mitigate floor and ceiling effects through techniques such as computer adaptive testing (ie, selection of questions based on a patient's prior responses).<sup>55</sup>

## Overall HRQOL in HCC Before and After Treatment

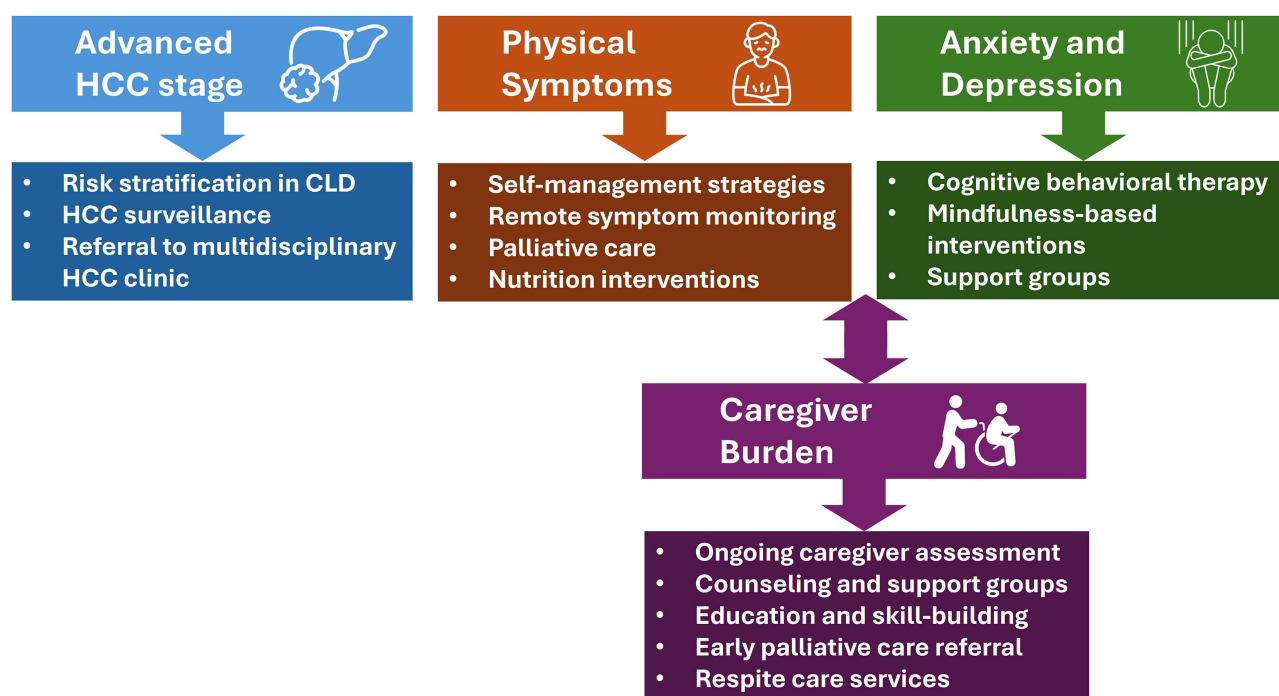
Prior to receiving treatment, patients with HCC report impaired HRQOL compared to the general population, particularly for physical, emotional and functional well-being.<sup>3,12,27,56–62</sup> Much of the diminished HRQOL results from symptoms such as fatigue, pain, loss of appetite and sleep disturbance (Figure 1). There are also data suggesting that HRQOL is associated with overall survival, independent of tumor stage and liver dysfunction.<sup>3</sup> Specifically, role functioning, defined as an individual's ability to perform usual daily activities, work and leisure activities, is a strong predictor of overall survival in HCC.<sup>63,64</sup> Other studies reported that physical symptoms (fatigue, pain, appetite loss, diarrhea) and physical functioning were associated with survival in patients with HCC.<sup>63,65–68</sup>

There are several clinical factors that influence HRQOL in HCC, including cancer stage, degree of underlying liver disease, and baseline performance status.<sup>3,56,60,69,70</sup> HCC treatments have variable effects on HRQOL: many treatments are associated with short-term worsening of symptoms but long-term improvement in HRQOL.<sup>3,26–28,71–90</sup> Potentially “curative” treatments including surgical resection, thermal ablation, and liver transplantation result in a HRQOL decline 2–10 weeks after therapy followed by return to baseline values at 3–4 months, and improvements above baseline HRQOL at 9 months.<sup>12,76,91</sup> Further, surgical resection results in better HRQOL scores compared to locoregional therapies.<sup>76</sup> However, there is a strong potential for selection bias given that patients selected for surgery are inherently healthier at baseline. Furthermore, a patient's knowledge that they are receiving a “curative” treatment may influence HRQOL reports. In studies directly comparing the effect of locoregional therapies on HRQOL, transarterial Y<sup>90</sup>-radioembolization (TARE) resulted in smaller decreases in HRQOL compared to transarterial chemoembolization (TACE), although these differences were not statistically significant.<sup>72,89</sup> Comparisons of locoregional therapies and systemic therapy have demonstrated higher HRQOL in patients treated with TARE compared to the oral multi-kinase inhibitor sorafenib in the weeks to months after treatment.<sup>88,92</sup> However, sorafenib has since been supplanted by newer, less toxic systemic therapies with improved HRQOL.<sup>93–95</sup> In the REFLECT trial, lenvatinib was shown to be non-inferior to sorafenib in overall survival and demonstrated delays in deterioration of fatigue, pain, and diarrhea scores.<sup>96</sup> More recently, combination immunotherapies (atezolizumab plus bevacizumab; single dose tremelimumab plus durvalumab) have been shown to not only improve overall survival compared with sorafenib but also prolong the time to deterioration across several symptom and functional domains, including role functioning and physical functioning.<sup>97,98</sup> Due to a push from the FDA to include PROs as study endpoints,<sup>99</sup> trials of systemic therapies for HCC now routinely assess the effects of treatments on PROs.<sup>79,96–98,100–104</sup> One compelling, yet unanswered, question is whether changes in PROs could be viewed as a therapeutic target of interest or whether PROs could potentially serve as a surrogate marker of efficacy.

## Potential Interventions to Improve HRQOL in HCC

There are several potential interventions that could improve HRQOL in HCC by addressing the factors underlying impaired HRQOL (Figure 2). Given influence of stage and treatment type on HRQOL, early detection of HCC may lead to improved PROs.<sup>12,56</sup> Improving the adoption of evidence-based screening for HCC in appropriately risk stratified patients with cirrhosis and chronic hepatitis B virus would increase the proportion of patients diagnosed with HCC at an earlier stage.<sup>93,105</sup> Additionally, referral of patients diagnosed with HCC to centers that can offer curative therapies including surgical resection and liver transplantation may improve these outcomes.<sup>93</sup> Ideally, patients should be seen in multidisciplinary HCC clinics, which are associated with higher proportion of patients receiving curative treatment, higher patient satisfaction, and improved overall survival.<sup>106–110</sup>





**Figure 2** Factors associated with poor HRQOL in HCC and potential interventions to address these factors.

Improved detection and management of physical symptoms, including through novel approaches such as remote symptom monitoring,<sup>8</sup> could help better address symptoms related to HCC, cirrhosis, and cancer treatments.<sup>3</sup> Symptom monitoring paired with self-management strategies and/or nurse navigation has the potential to improve symptom burden and, in turn, overall HRQOL. In metastatic cancer populations, remote PRO monitoring improves symptom burden, increases HRQOL, reduces health care utilization, and improves survival.<sup>19,111,112</sup> Qualitative work in the HCC population has demonstrated that a high proportion of patients with HCC are interested in remote symptom monitoring<sup>8</sup> and a pilot trial suggests that it is feasible to remotely monitor for liver-related decompensation events among patients with cirrhosis.<sup>113</sup> Remote monitoring of common HCC-related symptoms and decompensation events may therefore hold promise in reducing acute care utilization and improving symptom burden.

Depression and anxiety are common among patients with HCC and have a significant impact on overall HRQOL in HCC.<sup>3,114</sup> One systematic review reported that depressive and anxiety symptoms are prevalent in 28% and 40%, respectively.<sup>114</sup> The estimated incidence of depression is significantly higher in patients with HCC compared to the general population.<sup>114</sup> Interventions to address depression and anxiety symptoms that have been studied in HCC include cognitive-behavioral therapy (CBT), mindfulness-based interventions (eg, meditation and yoga), and support groups.<sup>57,114–117</sup> However, there remain significant gaps in our understanding of depression and anxiety in HCC given the heterogeneity in assessment tools, lack of longitudinal studies, and paucity of interventional trials.

An improved quality of life could also be achieved through patient empowerment and active participation in the decision-making process. This begins with patient education on HCC prognosis, treatment options, and side effects.<sup>115,118,119</sup> Patient education could elicit positive impacts on patients by reducing fear and uncertainty through knowledge on HCC diagnosis, prognosis, and setting realistic expectations to reduce anxiety stemming from the unknown.<sup>60,115,116</sup> Clinicians may further empower patients by facilitating active participation in decision-making to deliver preference-concordant care that may impact decisional satisfaction and treatment adherence.<sup>115,120,121</sup> Training patients in symptom management techniques helps directly improve physical and emotional well-being while simultaneously reinforcing a sense of agency and reducing feelings of helplessness.<sup>8,57,121–123</sup> Lastly, nutritional assessment can identify patients who may benefit from self-directed nutritional

support interventions (eg, branched-chain amino acid supplementation), which are associated with improvements in HRQOL in patients with HCC.<sup>124–128</sup>

Finally, the physical and mental burdens of both cirrhosis and HCC in addition to the need for frequent clinical assessment and retreatment result in a large burden on caregivers.<sup>129</sup> Caregivers express lack of preparedness, uncertainty, and information gaps regarding symptom interpretation, HCC disease course, and available treatments.<sup>13</sup> Caregivers specifically note uncertainty about how to interpret symptoms like confusion, disorientation, and fatigue and how to assess the relative contributions from HCC, cirrhosis, and non-liver comorbidities.<sup>13</sup> These burdens can result in social isolation, psychological distress, and impaired quality of life for caregivers.<sup>13</sup> The caregiver experience may be particularly challenging for patient–caregiver relationships that are strained at the time of HCC diagnosis. Ongoing caregiver assessment and consideration of the interventions outlined in [Figure 2](#) may help alleviate caregiver burden.

## Conclusion

In summary, HCC is a uniquely complex disease with symptoms and complications resulting from underlying cirrhosis, HCC, and cancer therapies. HCC is treated by several different therapies offered by different specialties, which range from curative options such as surgical resection and liver transplantation, to systemic therapies including the recently approved immunotherapy combinations generally prescribed by medical oncologists. Assessment of PROs provides patient experiential data that complements clinicians' observations and may help facilitate tailored treatment decisions, shared decision-making, early identification and alleviation of symptoms, psychosocial burden, and caregiver strain. There are several PRO measures that have been utilized to capture patient experiences with HCC in clinical and research settings. These instruments have varying levels of validation and tradeoffs, with the most robust HCC-specific validation for the EORTC QLQ-HCC18 and FACT-Hep instruments, based on the fact that these were specifically developed and validated in HCC patients, contain disease-specific symptoms, and are among the most commonly used HRQOL tools that have been used in HCC.<sup>3,12,130</sup> While disease-specific instruments are likely best equipped to capture HCC-, cirrhosis- and treatment-related symptoms, these instruments may not include all relevant symptoms and further PRO development and validation would be welcome. Patients with HCC have impaired physical, emotional, and functional well-being and significant symptom burden ([Figure 1](#)). Cancer stage, underlying liver disease severity, and baseline performance status are associated with PROs and, in turn, baseline PROs are associated with post-treatment survival. Several interventions exist that have the potential to improve HRQOL in HCC including risk-stratification/surveillance, referral to multidisciplinary teams, and targeted interventions for physical and emotional symptoms and caregiver burden. Increased utilization of PRO measures in research and adoption of PRO assessment and interventions in clinical practice are likely to improve health and treatment outcomes for patients with HCC.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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