Journal of Hepatocellular Carcinoma

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REVIEW

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.[1,2] 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.[3] 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.[4–8] Furthermore, there are several treatment options for HCC offered by different medical, radiological, or surgical subspecialties.[9] Treatment decisions are best made in the context of multi-disciplinary discussions in which tradeoffs among benefits, risks, inconvenience, costs, and patient preferences are considered.[9] However, many patients face barriers to accessing multidisciplinary care and co-located HCC clinics with multiple specialists on staff are unavailable at most centers.[9–11] 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.[12,13] 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.[14] 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

Received: 1 December 2024
Accepted: 28 February 2025
Published: 5 March 2025

frequency, and at higher intensity suggesting that clinicians underestimate symptom burden.[15–17] Discrepancies are particularly common for more subjective symptoms such as fatigue and confusion, commonly encountered in patients with HCC.[3,18] 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.[3,14,19] However, in the clinical setting, administrative requirements and costs are potential barriers to their adoption.[20] Progress has been made, however, to encourage PRO collection in routine clinical care, such as alternative payment models that require the incorporation of PROs.[21,22] Research and early clinical experiences suggest that PRO measures enhance care.[3] 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.[3]

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.[23] 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.[24] 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.[25] 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.[23] Specifically, a responsive measure should worsen if a patients 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.[26–28] 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.[29] 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.[30,31] 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.[31]

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.[32] 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.[3,8]

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

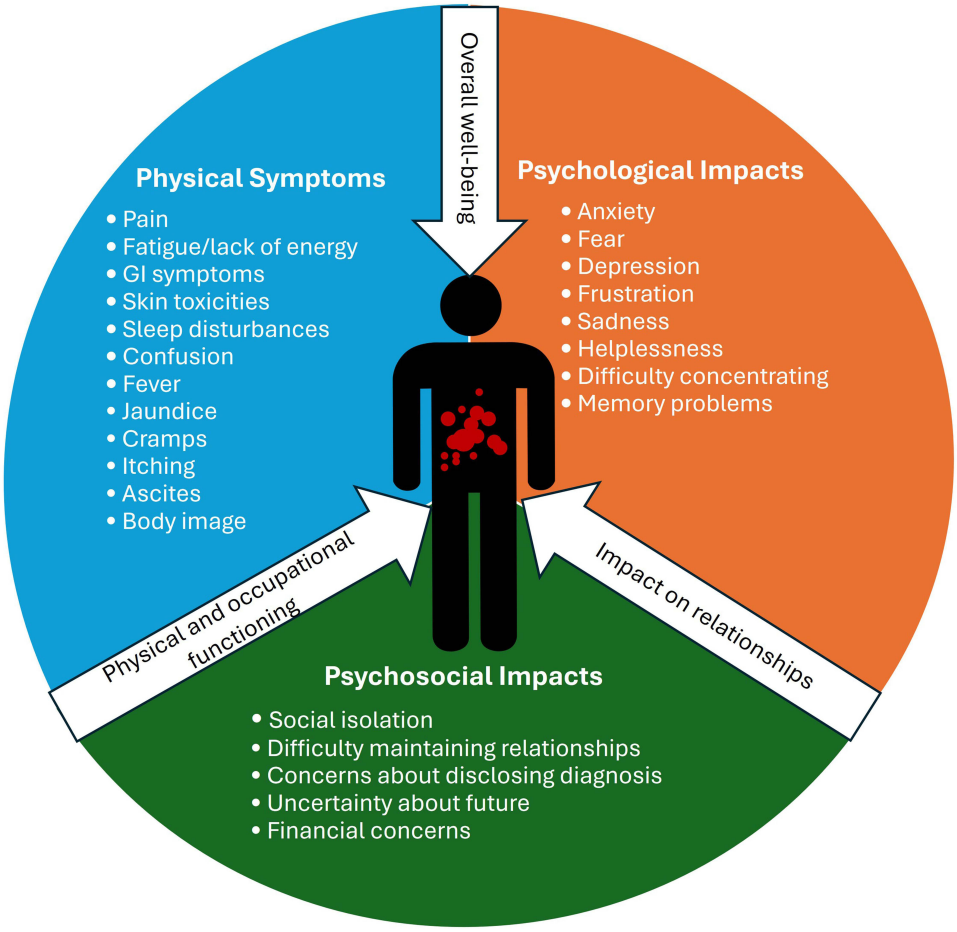

Figure 1 The impact of HCC and its treatments on patient well-being.

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.[14,51–53] 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.[53,54] 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).[3] 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).[3]

https://doi.org/10.2147/JHC.S347929

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[33]	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: • Widely used • Well-validated • Good for comparing to general population Cons: • Not specific for liver disease or cancer • Less sensitive for HCC-specific issues • Less focus on symptoms
	Short Form (SF)-12	Ware[34]	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[35]	Generic instrument that measures five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.	Pros: • Brevity • Provides a utility score for quality-adjusted life year scores • Can be used across a wide range of diseases Cons: • Limited scope • Not disease-specific • Less sensitive and responsive to HCC-related concerns
	World Health Organization Quality of Life (WHOQOL)-100	WHOQOL Group[36]	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: • Comprehensive with multiple domains • Well-established tool for measuring HRQOL • Available in more than 40 languages allowing for cross-cultural comparisons Cons: • Lengthy (100 items) • Difficult to administer and interpret • Not disease specific
	World Health Organization Quality of Life (WHOQOL)-BREF	WHOQOL Group[37]	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

https://doi.org/10.2147/JHC.S347929

	Spitzer Quality of Life Index (SQLI)	Spitzer[38]	Brief instrument measuring a patient's overall perception of their quality of life across five domains: activity, daily living, health, support, and outlook	Pros: • Short and easy to administer • Designed to be used by physicians for clinical assessments and decision-making • Good inter-rater reliability Cons: • Limited scope and scoring range • May not capture the full spectrum of the patient's experience • Not patient-reported
	Patient-Reported Outcomes Measurement Information System (PROMIS)-29	Hays[39]	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	Pros: • Efficient and highly usable • Comprehensive scope and depth • Standardized scoring • Customizable Cons: • General measure • Missing domains for patients with liver disease • Potential floor and ceiling effects
	Edmonton Symptom Assessment Scale (ESAS)	Watanabe[40]	Instrument used to assess common symptoms experienced in advance illness including pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath	Pros: • Brevity and ease of use • Comprehensive assessment of symptoms • Validated in patients with cirrhosis Cons: • Not disease-specific • Does not capture all symptoms common in patients with liver disease or HCC • Less validation than other generic measures

(*Continued*)

https://doi.org/10.2147/JHC.S347929

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Table 1 (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[41]	Instrument assessing physical, role, emotional, cognitive, and social functioning, as well as symptoms like fatigue, nausea, and pain	Pros: • Comprehensive assessment of generic- and cancer-specific issues • Widely used and validated • Simple scoring (0–100) Cons: • Unclear interpretation of clinical meaningfulness • Burden on patients
	Functional Assessment of Cancer Therapy - General (FACT-G)	Cella[42]	Questionnaire focusing on physical, social, emotional, and functional well-being	Pros: • Easy to administer and score • Good reliability and validity • Sensitive to clinical changes and well-established clinically meaningful differences Cons: • Limited coverage of social quality of life • Not comprehensive for all symptoms common in cirrhosis and HCC
	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)	Basch[43]	Standardized measurement system designed to capture patient-reported symptomatic adverse events experienced during cancer treatment	Pros: • Includes a comprehensive library of symptomatic adverse events and can be adapted to setting • Frequency, severity and interference of AEs can be assessed • Multiple administration modes Cons: • It can be difficult to choose which items to select • Focuses on symptoms but no other components of HRQOL
	Brief Pain Inventory-Short Form	Cleeland[44]	Instrument to measure pain location, pain severity (worst, least, average, right now), improvement from pain medications and pain interference	Pros: • Quick and easy completion • Clear use for assessing pain Cons: • Limited scope • May not capture complexity of pain • Not specific to HCC
	MD Anderson Symptom Inventory (MDASI)	Cleeland[45]	Multi-symptom assessment tool that assesses several symptoms items and interference with physical activity, social activity, enjoyment of life and mood	Pros: • Validated for measuring severity of symptoms in cancer patients • Good psychometric properties Cons: • Limited scope, particularly for HCC • Assesses the amount and severity of symptoms, but not symptom distress

	Memorial Symptom Assessment Scale (MSAS)	Portenoy[46]	Assesses symptom frequency, severity and distress or bother of 32 symptoms	Pros: ● Measures multiple dimensions of a wide range of symptoms ● Well established psychometric properties ● Takes 10–15 minutes to complete Cons: ● No global score due to multiple subscores ● No comparison to normative sample ● Not commonly used, particularly for HCC
HCC-Specific	European Organization for. Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-HCC18	Blazeby[47]	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	Pros: ● HCC-specific focused survey that complements EORTC QLQ-C30 ● Patient-centered development in HCC ● Cross-cultural validity Cons: ● Associated with higher respondent burden ● Interpretation complicated by scoring system
	Functional Assessment of Cancer Therapy - Hepatobiliary (FACT-Hep)	Heffernan[48]	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	Pros: ● Disease-specific and comprehensive ● Validated in patients with HCC ● Sensitive to changes in disease progression and treatment response Cons: ● High respondent burden ● May not capture psychological or spiritual aspects of HCC
	FACT Hepatobiliary Symptom Index (FHSI-8)	Cella[49]	Abbreviated symptom index derived from the FACT-Hep, focusing on key symptoms of hepatobiliary cancers	Pros: ● Brief and efficient assessment of key symptoms ● Designed for use in clinical trials and routine clinical practice Cons: ● Limited scope ● Loss of precision compared to FACT-Hep
	National Comprehensive Cancer Network (NCCN)-Functional Assessment of Cancer Therapy–Hepatobiliary–Pancreatic Symptom Index (NFHSI-18)	Butt[50]	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	Pros: ● Focused on symptoms experienced by patients with hepato-biliary and pancreatic cancers ● Multi-dimensional and with comprehensive symptom coverage Cons: ● More burdensome than other symptom measures (eg, FHSI-8) ● Does not capture social or emotional well-being

https://doi.org/10.2147/JHC.S347929

Finally, the appropriate selection of a PRO measure may hinge on its floor and ceiling effects.[23] 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).[55]

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.[3,12,27,56–62] 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.[3] 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.[63,64] Other studies reported that physical symptoms (fatigue, pain, appetite loss, diarrhea) and physical functioning were associated with survival in patients with HCC.[63,65–68]

There are several clinical factors that influence HRQOL in HCC, including cancer stage, degree of underlying liver disease, and baseline performance status.[3,56,60,69,70] HCC treatments have variable effects on HRQOL: many treatments are associated with short-term worsening of symptoms but long-term improvement in HRQOL.[3,26–28,71–90] 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.[12,76,91] Further, surgical resection results in better HRQOL scores compared to locoregional therapies.[76] 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^{90}-radioembolization (TARE) resulted in smaller decreases in HRQOL compared to transarterial chemoembolization (TACE), although these differences were not statistically significant.[72,89] 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.[88,92] However, sorafenib has since been supplanted by newer, less toxic systemic therapies with improved HRQOL.[93–95] 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.[96] 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.[97,98] Due to a push from the FDA to include PROs as study endpoints,[99] trials of systemic therapies for HCC now routinely assess the effects of treatments on PROs.[79,96–98,100–104] 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.[12,56] 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.[93,105] Additionally, referral of patients diagnosed with HCC to centers that can offer curative therapies including surgical resection and liver transplantation may improve these outcomes.[93] 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.[106–110]

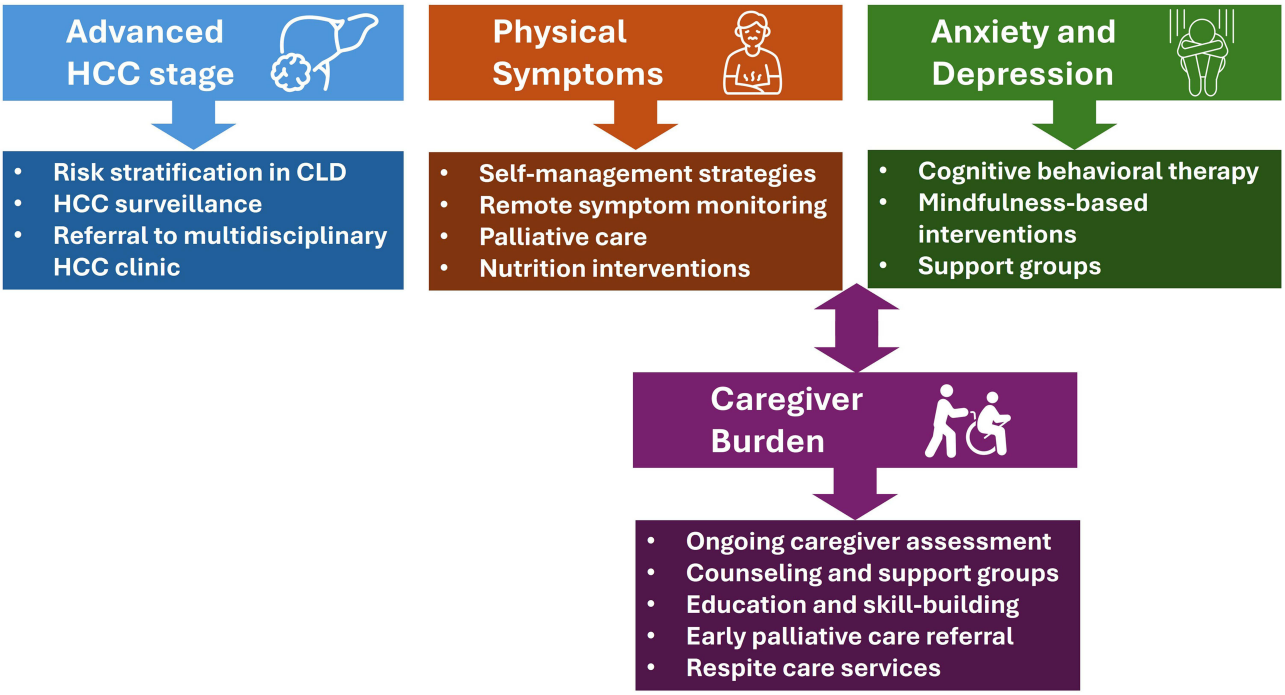

Figure 2 Factors associated with poor HRQOL in HCC and potential interventions to address these factors.

Improved detection and management of physical symptoms, including through novel approaches such as remote symptom monitoring,[8] could help better address symptoms related to HCC, cirrhosis, and cancer treatments.[3] 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.[19,111,112] Qualitative work in the HCC population has demonstrated that a high proportion of patients with HCC are interested in remote symptom monitoring[8] and a pilot trial suggests that it is feasible to remotely monitor for liver-related decompensation events among patients with cirrhosis.[113] 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.[3,114] One systematic review reported that depressive and anxiety symptoms are prevalent in 28% and 40%, respectively.[114] The estimated incidence of depression is significantly higher in patients with HCC compared to the general population.[114] 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.[57,114–117] 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.[115,118,119] 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.[60,115,116] 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.[115,120,121] 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.[8,57,121–123] 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.[124–128]

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.[129] Caregivers express lack of preparedness, uncertainty, and information gaps regarding symptom interpretation, HCC disease course, and available treatments.[13] 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.[13] These burdens can result in social isolation, psychological distress, and impaired quality of life for caregivers.[13] 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.[3,12,130] 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.

Funding

This research was supported in part by an AASLD Clinical, Translational and Outcomes Award from the AASLD Foundation (AMM).

Disclosure

AMM: Consultant for TARGET RWE, Intercept Pharmaceuticals, personal fees from Eisai, personal fees from Intercept, and IDEOlogy Health. Research funding (to institution) from DCN Diagnostics. ASB: Consultant for Target-RWE, Madrigal, Mirum, Life-Edit, Boehringer Ingelheim, Merck. LIW: Consultant for Bristol Myers Squibb, Inc., unrelated to this research. The authors report no other conflicts of interest in this work.

References

1. Llovet JM, Kelley RK, Villanueva A. et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6. doi:10.1038/s41572-020-00240-3
2. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004;127(5 Suppl 1):S35–50. doi:10.1053/j.gastro.2004.09.014
3. Serper M, Parikh ND, Thiele G, et al. Patient-reported outcomes in HCC: a scoping review by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. *Hepatology*. 2022;76(1):251–274. doi:10.1002/hep.32313
4. Mohammed MAA, Khalaf MH, Liang T, et al. Albumin-Bilirubin Score: an Accurate Predictor of Hepatic Decompensation in High-Risk Patients Undergoing Transarterial Chemoembolization for Hepatocellular Carcinoma. *J Vasc Interv Radiol*. 2018;29(11):1527–1534e1. doi:10.1016/j.jvir.2018.06.016
5. Ranganathan S, Gabr A, Entezari P, et al. Radioembolization for Intermediate-Stage Hepatocellular Carcinoma Maintains Liver Function and Permits Systemic Therapy at Progression. *J Vasc Interv Radiol*. 2023;34(6):968–975. doi:10.1016/j.jvir.2022.11.036
6. Reincke M, Schultheiss M, Doppler M, et al. Hepatic decompensation after transarterial radioembolization: a retrospective analysis of risk factors and outcome in patients with hepatocellular carcinoma. *Hepatol Commun*. 2022;6(11):3223–3233. doi:10.1002/hep4.2072
7. Scheiner B, Ulbrich G, Mandorfer M, et al. Short- and long-term effects of transarterial chemoembolization on portal hypertension in patients with hepatocellular carcinoma. *United Eur Gastroenterol J*. 2019;7(6):850–858. doi:10.1177/2050640619840199
8. Moon AM, Cook S, Swier RM, et al. Patient-reported symptoms and interest in symptom monitoring in HCC treated with locoregional therapies: a qualitative study. *Hepatol Commun*. 2023;7(11). doi:10.1097/HC9.0000000000000315
9. Byrd K, Alqahtani S, Yopp AC, Singal AG. Role of Multidisciplinary Care in the Management of Hepatocellular Carcinoma. *Semin Liver Dis*. 2021;41(1):1–8. doi:10.1055/s-0040-1719178
10. Moon AM, Sanoff HK, Chang Y, et al. Medicare/Medicaid Insurance, Rurality, and Black Race Associated With Provision of Hepatocellular Carcinoma Treatment and Survival. *J Natl Compr Canc Netw*. 2021;19(3):285–293. doi:10.6004/jnccn.2020.7616
11. El Dahan K S, Reczek A, Daher D, et al. Multidisciplinary care for patients with HCC: a systematic review and meta-analysis. *Hepatol Commun*. 2023;7(5). doi:10.1097/HC9.0000000000000143
12. Fan SY, Eiser C, Ho MC. Health-related quality of life in patients with hepatocellular carcinoma: a systematic review. *Clin Gastroenterol Hepatol*. 2010;8(7):559–64e1–10. doi:10.1016/j.cgh.2010.03.008
13. Hansen L, Rosenkranz SJ, Wherity K, Sasaki A. Living With Hepatocellular Carcinoma Near the End of Life: family Caregivers' Perspectives. *Oncol Nurs Forum*. 2017;44(5):562–570. doi:10.1188/17.ONF.562-570
14. U.S.Department of Health and Human Services FDA. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes*. 2006;4(1):79. doi:10.1186/1477-7525-4-79.
15. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. *J Natl Cancer Inst*. 2009;101(23):1624–1632. doi:10.1093/jnci/djp386
16. Basch E, Iasonos A, McDonough T, et al. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol*. 2006;7(11):903–909. doi:10.1016/S1470-2045(06)70910-X
17. Leith A, Kiiskinen U, Girvan AC, et al. Physician- and patient-reported symptom concordance and association with quality of life in hepatocellular carcinoma. *Future Oncol*. 2022;18(33):3727–3740. doi:10.2217/fon-2022-0202
18. Moon AM, Kim HP, Jiang Y, et al. Systematic Review and Meta-Analysis on the Effects of Lactulose and Rifaximin on Patient-Reported Outcomes in Hepatic Encephalopathy. *Am J Gastroenterol*. 2023;118(2):284–293. doi:10.14309/ajg.0000000000002008
19. Basch E, Schrag D, Henson S, et al. Effect of Electronic Symptom Monitoring on Patient-Reported Outcomes Among Patients With Metastatic Cancer: a Randomized Clinical Trial. *JAMA*. 2022;327(24):2413–2422. doi:10.1001/jama.2022.9265
20. Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med*. 2010;362(10):865–869. doi:10.1056/NEJMp0911494
21. Basch E. Evaluating Alternative Payment Models in Oncology. *JAMA*. 2017;317(20):2123–2124. doi:10.1001/jama.2017.3028
22. Gettel CJ, Suter LG, Bagshaw K, et al. Patient-Reported Outcome-Based Performance Measures in Alternative Payment Models: current Use, Implementation Barriers, and Principles to Succeed. *Value Health*. 2024;27(2):199–205. doi:10.1016/j.jval.2023.10.017
23. Rothrock NE, Kaiser KA, Cella D. Developing a valid patient-reported outcome measure. *Clin Pharmacol Ther*. 2011;90(5):737–742. doi:10.1038/clpt.2011.195
24. U.S. Food and Drug Administration. Patient-Focused Drug Development: selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments. Available from: https://www.fda.gov/media/159500/download. Accessed November 25, 2024.
25. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol*. 2010;63(7):737–745. doi:10.1016/j.jclinepi.2010.02.006
26. Lee LJ, Chen CH, Yao G, et al. Quality of life in patients with hepatocellular carcinoma received surgical resection. *J Surg Oncol*. 2007;95 (1):34–39. doi:10.1002/jso.20374
27. Chie WC, Blazeby JM, Hsiao CF, et al. Differences in health-related quality of life between European and Asian patients with hepatocellular carcinoma. *Asia Pac J Clin Oncol*. 2017;13(5):e304–e311. doi:10.1111/ajco.12464
28. Hartrumpf KJ, Marquardt S, Werncke T, et al. Quality of life in patients undergoing repetitive TACE for the treatment of intermediate stage HCC. *J Cancer Res Clin Oncol*. 2018;144(10):1991–1999. doi:10.1007/s00432-018-2704-7
29. McGlothlin AE, Lewis RJ. Minimal clinically important difference: defining what really matters to patients. *JAMA*. 2014;312(13):1342–1343. doi:10.1001/jama.2014.13128
30. Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. *J Chronic Dis*. 1987;40 (2):171–178. doi:10.1016/0021-9681(87)90069-5
31. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10(4):407–415. doi:10.1016/0197-2456(89)90005-6
32. U.S. Food and Drug Administration. Patient-Focused Drug Development: incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making. Available from: https://www.fda.gov/media/166830/download. Accessed November 25, 2024.
33. Ware Jr JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). *Med Care*. 1992;30(6):473–483. doi:10.1097/00005650-199206000-00002

34. Ware Jr J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220–233. doi:10.1097/00005650-199603000-00003
35. EuroQol G. EuroQol–a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199–208.
36. Group W, WHOQOL Group. Development of the WHOQOL: rationale and Current Status. *Int J Mental Health*. 1994;23(3):24–56. doi:10.1080/00207411.1994.11449286
37. Development of the World Health Organization WHOQOL-BREF. quality of life assessment. The WHOQOL Group. *Psychol Med*. 1998;28 (3):551–558. doi:10.1017/s0033291798006667.
38. Spitzer WO, Dobson AJ, Hall J, et al. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. *J Chronic Dis*. 1981;34(12):585–597. doi:10.1016/0021-9681(81)90058-8
39. Hays RD, Spritzer KL, Schalet BD, Cella D. PROMIS((R))-29 v2.0 profile physical and mental health summary scores. *Qual Life Res*. 2018;27 (7):1885–1891. doi:10.1007/s11136-018-1842-3
40. Watanabe SM, Nekolaichuk C, Beaumont C, Johnson L, Myers J, Strasser F. A multicenter study comparing two numerical versions of the Edmonton Symptom Assessment System in palliative care patients. *J Pain Symptom Manage*. 2011;41(2):456–468. doi:10.1016/j.jpainsymman.2010.04.020
41. Fayers P, Bottomley A, Group EQoL, Quality of Life U. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. *Eur J Cancer*. 2002;38(Suppl 4):S125–33. doi:10.1016/s0959-8049(01)00448-8
42. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570–579. doi:10.1200/JCO.1993.11.3.570
43. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst*. 2014;106(9):dju244–dju244. doi:10.1093/jnci/dju244
44. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap*. 1994;23(2):129–138.
45. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer*. 2000;89(7):1634–1646. doi:10.1002/1097-0142(20001001)89:7<1634::aid-cncr29>3.0.co;2-v
46. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer*. 1994;30A(9):1326–1336. doi:10.1016/0959-8049(94)90182-1
47. Blazeby JM, Currie E, Zee BC, et al. Development of a questionnaire module to supplement the EORTC QLQ-C30 to assess quality of life in patients with hepatocellular carcinoma, the EORTC QLQ-HCC18. *Eur J Cancer*. 2004;40(16):2439–2444. doi:10.1016/j.ejca.2004.06.033
48. Heffernan N, Cella D, Webster K, et al. Measuring health-related quality of life in patients with hepatobiliary cancers: the functional assessment of cancer therapy-hepatobiliary questionnaire. *J Clin Oncol*. 2002;20(9):2229–2239. doi:10.1200/JCO.2002.07.093
49. Cella D, Paul D, Yount S, et al. What are the most important symptom targets when treating advanced cancer? A survey of providers in the National Comprehensive Cancer Network (NCCN). *Cancer Invest*. 2003;21(4):526–535. doi:10.1081/cnv-120022366
50. Butt Z, Parikh ND, Beaumont JL, et al. Development and validation of a symptom index for advanced hepatobiliary and pancreatic cancers: the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy (NCCN-FACT) Hepatobiliary-Pancreatic Symptom Index (NFHSI). *Cancer*. 2012;118(23):5997–6004. doi:10.1002/cncr.27588
51. Crossnohere NL, Brundage M, Calvert MJ, et al. International guidance on the selection of patient-reported outcome measures in clinical trials: a review. *Qual Life Res*. 2021;30(1):21–40. doi:10.1007/s11136-020-02625-z
52. Kaneyasu T, Hoshino E, Naito M, et al. How to select and understand guidelines for patient-reported outcomes: a scoping review of existing guidance. *BMC Health Serv Res*. 2024;24(1):334. doi:10.1186/s12913-024-10707-8
53. Al Sayah F, Jin X, Johnson JA. Selection of patient-reported outcome measures (PROMs) for use in health systems. *J Patient Rep Outcomes*. 2021;5(Suppl 2):99. doi:10.1186/s41687-021-00374-2
54. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care*. 1989;27(3 Suppl):S217–32. doi:10.1097/00005650-198903001-00018
55. Petersen MA, Aaronson NK, Arraras JI, et al. The EORTC CAT Core-The computer adaptive version of the EORTC QLQ-C30 questionnaire. *Eur J Cancer*. 2018;100:8–16. doi:10.1016/j.ejca.2018.04.016
56. Bianchi G, Loguercio C, Sgarbi D, et al. Reduced quality of life of patients with hepatocellular carcinoma. *Dig Liver Dis*. 2003;35(1):46–54. doi:10.1016/S1590-8658(02)00011-7
57. Chen NY, Chen KH, Wang YW, Tsai HH, Lee WC, Weng LC. The impact of symptom distress on health-related quality of life in liver cancer patients receiving arterial chemoembolization: the mediating role of hope. *BMC Gastroenterol*. 2022;22(1):456. doi:10.1186/s12876-022-02529-x
58. Hansen L, Rosenkranz SJ, Vaccaro GM, Chang MF. Patients With Hepatocellular Carcinoma Near the End of Life: a Longitudinal Qualitative Study of Their Illness Experiences. *Cancer Nurs*. 2015;38(4):E19–27. doi:10.1097/NCC.0000000000000188
59. Kaiser K, Mallick R, Butt Z, Mulcahy MF, Benson AB, Cella D. Important and relevant symptoms including pain concerns in hepatocellular carcinoma (HCC): a patient interview study. *Support Care Cancer*. 2014;22(4):919–926. doi:10.1007/s00520-013-2039-5
60. Kondo Y, Yoshida H, Tateishi R, et al. Health-related quality of life of chronic liver disease patients with and without hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2007;22(2):197–203. doi:10.1111/j.1440-1746.2006.04456.x
61. Steel JL, Chopra K, Olek MC, Carr BI. Health-related quality of life: hepatocellular carcinoma, chronic liver disease, and the general population. *Qual Life Res*. 2007;16(2):203–215. doi:10.1007/s11136-006-9111-2
62. Verma M, Paik JM, Younossi I, Tan D, Abdelaal H, Younossi ZM. The impact of hepatocellular carcinoma diagnosis on patients' health-related quality of life. *Cancer Med*. 2021;10(18):6273–6281. doi:10.1002/cam4.4166
63. Diouf M, Filleron T, Barbare JC, et al. The added value of quality of life (QoL) for prognosis of overall survival in patients with palliative hepatocellular carcinoma. *J Hepatol*. 2013;58(3):509–521. doi:10.1016/j.jhep.2012.11.019
64. Meier A, Yopp A, Mok H, Kandunoori P, Tiro J, Singal AG. Role functioning is associated with survival in patients with hepatocellular carcinoma. *Qual Life Res*. 2015;24(7):1669–1675. doi:10.1007/s11136-014-0895-1
65. Sternby Eilard M, Hagstrom H, Mortensen KE, et al. Quality of life as a prognostic factor for survival in hepatocellular carcinoma. *Liver Int*. 2018;38(5):885–894. doi:10.1111/liv.13593

66. Li L, Mo FK, Chan SL, et al. Prognostic values of EORTC QLQ-C30 and QLQ-HCC18 index-scores in patients with hepatocellular carcinoma - clinical application of health-related quality-of-life data. *BMC Cancer*. 2017;17(1):8. doi:10.1186/s12885-016-2995-5
67. Yeo W, Mo FK, Koh J, et al. Quality of life is predictive of survival in patients with unresectable hepatocellular carcinoma. *Ann Oncol*. 2006;17 (7):1083–1089. doi:10.1093/annonc/mdl065
68. Gmur A, Kolly P, Knopfli M, Dufour JF. FACT-Hep increases the accuracy of survival prediction in HCC patients when added to ECOG Performance Status. *Liver Int*. 2018;38(8):1468–1474. doi:10.1111/liv.13711
69. Li L, Mo F, Hui EP, et al. The association of liver function and quality of life of patients with liver cancer. *BMC Gastroenterol*. 2019;19(1):66. doi:10.1186/s12876-019-0984-2
70. Qiao CX, Zhai XF, Ling CQ, et al. Health-related quality of life evaluated by tumor node metastasis staging system in patients with hepatocellular carcinoma. *World J Gastroenterol*. 2012;18(21):2689–2694. doi:10.3748/wjg.v18.i21.2689
71. Brunocilla PR, Brunello F, Carucci P, et al. Sorafenib in hepatocellular carcinoma: prospective study on adverse events, quality of life, and related feasibility under daily conditions. *Med Oncol*. 2013;30(1):345. doi:10.1007/s12032-012-0345-2
72. Salem R, Gilbertsen M, Butt Z, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. *Clin Gastroenterol Hepatol*. 2013;11(10):1358–1365e1. doi:10.1016/j.cgh.2013.04.028
73. Poon RT, Fan ST, Yu WC, Lam BK, Chan FY, Wong J. A prospective longitudinal study of quality of life after resection of hepatocellular carcinoma. *Arch Surg*. 2001;136(6):693–699. doi:10.1001/archsurg.136.6.693
74. Huang G, Chen X, Lau WY, et al. Quality of life after surgical resection compared with radiofrequency ablation for small hepatocellular carcinomas. *Br J Surg*. 2014;101(8):1006–1015. doi:10.1002/bjs.9539
75. Wang YB, Chen MH, Yan K, Yang W, Dai Y, Yin SS. Quality of life after radiofrequency ablation combined with transcatheter arterial chemoembolization for hepatocellular carcinoma: comparison with transcatheter arterial chemoembolization alone. *Qual Life Res*. 2007;16 (3):389–397. doi:10.1007/s11136-006-9133-9
76. Toro A, Pulvirenti E, Palermo F, Di Carlo I. Health-related quality of life in patients with hepatocellular carcinoma after hepatic resection, transcatheter arterial chemoembolization, radiofrequency ablation or no treatment. *Surg Oncol*. 2012;21(1):e23–30. doi:10.1016/j.suronc.2011.10.005
77. Liu J, Wang Y, Zhang D, Liu B, Ou Q. Comparison of survival and quality of life of hepatectomy and thrombectomy using total hepatic vascular exclusion and chemotherapy alone in patients with hepatocellular carcinoma and tumor thrombi in the inferior vena cava and hepatic vein. *Eur J Gastroenterol Hepatol*. 2012;24(2):186–194. doi:10.1097/MEG.0b013e32834dda64
78. Hinrichs JB, Hasdemir DB, Nordlohne M, et al. Health-Related Quality of Life in Patients with Hepatocellular Carcinoma Treated with Initial Transarterial Chemoembolization. *Cardiovasc Intervent Radiol*. 2017;40(10):1559–1566. doi:10.1007/s00270-017-1681-6
79. Chau I, Peck-Radosavljevic M, Borg C, et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib: patient-focused outcome results from the randomised Phase III REACH study. *Eur J Cancer*. 2017;81:17–25. doi:10.1016/j.ejca.2017.05.001
80. Cao W, Li J, Hu C, et al. Symptom clusters and symptom interference of HCC patients undergoing TACE: a cross-sectional study in China. *Support Care Cancer*. 2013;21(2):475–483. doi:10.1007/s00520-012-1541-5
81. Wible BC, Rilling WS, Drescher P, et al. Longitudinal quality of life assessment of patients with hepatocellular carcinoma after primary transarterial chemoembolization. *J Vasc Interv Radiol*. 2010;21(7):1024–1030. doi:10.1016/j.jvir.2010.03.005
82. Chiu CC, Lee KT, Wang JJ, et al. Preoperative Health-Related Quality of Life Predicts Minimal Clinically Important Difference and Survival after Surgical Resection of Hepatocellular Carcinoma. *J Clin Med*. 2019;8(5):576. doi:10.3390/jcm8050576
83. He Q, Jiang JJ, Jiang YX, Wang WT, Yang L, Liver Surgery G. Health-Related Quality of Life Comparisons After Radical Therapy for Early-Stage Hepatocellular Carcinoma. *Transplant Proc*. 2018;50(5):1470–1474. doi:10.1016/j.transproceed.2018.04.041
84. Shomura M, Kagawa T, Okabe H, et al. Longitudinal alterations in health-related quality of life and its impact on the clinical course of patients with advanced hepatocellular carcinoma receiving sorafenib treatment. *BMC Cancer*. 2016;16(1):878. doi:10.1186/s12885-016-2908-7
85. Shun SC, Chiou JF, Lai YH, et al. Changes in quality of life and its related factors in liver cancer patients receiving stereotactic radiation therapy. *Support Care Cancer*. 2008;16(9):1059–1065. doi:10.1007/s00520-007-0384-y
86. Hassanin TM, Fouad Y, Hassnine A, Eisawy M, Farag N, Abdel Ghany W. Quality of Life after Transcatheter Arterial Chemoembolization Combined with Radiofrequency Ablation in Patients with Unresectable Hepatocellular Carcinoma Compared with Transcatheter Arterial Chemoembolization alone. *Asian Pac J Cancer Prev*. 2021;22(4):1255–1261. doi:10.31557/APJCP.2021.22.4.1255
87. Loffroy R, Ronot M, Greget M, et al. Short-term Safety and Quality of Life Outcomes Following Radioembolization in Primary and Secondary Liver Tumours: a Multi-centre Analysis of 200 Patients in France. *Cardiovasc Intervent Radiol*. 2021;44(1):36–49. doi:10.1007/s00270-020-02643-x
88. Pereira H, Bouattour M, Dioguardi Burgio M, et al. Health-related quality of life in locally advanced hepatocellular carcinoma treated by either radioembolisation or sorafenib (SARAH trial). *Eur J Cancer*. 2021;154:46–56. doi:10.1016/j.ejca.2021.05.032
89. Kirchner T, Marquardt S, Werncke T, et al. Comparison of health-related quality of life after transarterial chemoembolization and transarterial radioembolization in patients with unresectable hepatocellular carcinoma. *Abdom Radiol*. 2019;44(4):1554–1561. doi:10.1007/s00261-018-1802-y
90. Iwata H, Ogino H, Hattori Y, et al. Image-Guided Proton Therapy for Elderly Patients with Hepatocellular Carcinoma: high Local Control and Quality of Life Preservation. *Cancers*. 2021;13(2):219. doi:10.3390/cancers13020219
91. Lei JY, Yan LN, Wang WT, Zhu JQ, Li DJ. Health-Related Quality of Life and Psychological Distress in Patients With Early-Stage Hepatocellular Carcinoma After Hepatic Resection or Transplantation. *Transplant Proc*. 2016;48(6):2107–2111. doi:10.1016/j.transproceed.2016.04.012
92. Agirrezabal I, Brennan VK, Colaone F, et al. Transarterial Radioembolization Versus Atezolizumab-Bevacizumab in Unresectable Hepatocellular Carcinoma: a Matching-Adjusted Indirect Comparison of Time to Deterioration in Quality of Life. *Adv Ther*. 2022;39 (5):2035–2051. doi:10.1007/s12325-022-02099-0
93. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78(6):1922–1965. doi:10.1097/HEP.0000000000000466

94. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. *NEJM Evid*. 2022;1(8): EVIDoa2100070. doi:10.1056/EVIDoa2100070
95. Finn RS, Qin S, Ikeda K, et al. IMbrave150: updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol*. 2021;39(3 supplement):267. doi:10.1200/JCO.2021.39.3_suppl.267
96. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised Phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–1173. doi:10.1016/S0140-6736(18)30207-1
97. Sangro B, Galle PR, Kelley RK, et al. Patient-Reported Outcomes From the Phase III HIMALAYA Study of Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. *J Clin Oncol*. 2024;42(23):2790–2799. doi:10.1200/JCO.23.01462
98. Galle PR, Finn RS, Qin S, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(7):991–1001. doi:10.1016/S1470-2045(21)00151-0
99. Basch E, Geoghegan C, Coons SJ, et al. Patient-Reported Outcomes in Cancer Drug Development and US Regulatory Review: perspectives From Industry, the Food and Drug Administration, and the Patient. *JAMA Oncol*. 2015;1(3):375–379. doi:10.1001/jamaoncol.2015.0530
100. Ryoo BY, Merle P, Kulkarni AS, et al. Health-related quality-of-life impact of pembrolizumab versus best supportive care in previously systemically treated patients with advanced hepatocellular carcinoma: KEYNOTE-240. *Cancer*. 2021;127(6):865–874. doi:10.1002/cncr.33317
101. Vogel A, Qin S, Kudo M, et al. Lenvatinib versus sorafenib for first-line treatment of unresectable hepatocellular carcinoma: patient-reported outcomes from a randomised, open-label, non-inferiority, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2021;6(8):649–658. doi:10.1016/S2468-1253(21)00110-2
102. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020;382 (20):1894–1905. doi:10.1056/NEJMoa1915745
103. Zhu AX, Nipp RD, Finn RS, et al. Ramucirumab in the second-line for patients with hepatocellular carcinoma and elevated alpha-fetoprotein: patient-reported outcomes across two randomised clinical trials. *ESMO Open*. 2020;5(4):e000797. doi:10.1136/esmoopen-2020-000797
104. Kudo M, Galle PR, Llovet JM, et al. Ramucirumab in elderly patients with hepatocellular carcinoma and elevated alpha-fetoprotein after sorafenib in REACH and REACH-2. *Liver Int*. 2020;40(8):2008–2020. doi:10.1111/liv.14462
105. Singal AG, Zhang E, Narasimman M, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: a meta-analysis. *J Hepatol*. 2022;77(1):128–139. doi:10.1016/j.jhep.2022.01.023
106. Serper M, Taddei TH, Mehta R, et al. Association of Provider Specialty and Multidisciplinary Care With Hepatocellular Carcinoma Treatment and Mortality. *Gastroenterology*. 2017;152(8):1954–1964. doi:10.1053/j.gastro.2017.02.040
107. Chang TT, Sawhney R, Monto A, et al. Implementation of a multidisciplinary treatment team for hepatocellular cancer at a Veterans Affairs Medical Center improves survival. *HPB*. 2008;10(6):405–411. doi:10.1080/13651820802356572
108. Litton G, Kane D, Clay G, Kruger P, Belnap T, Parkinson B. Multidisciplinary cancer care with a patient and physician satisfaction focus. *J Oncol Pract*. 2010;6(6):e35–7. doi:10.1200/JOP.2010.000028
109. Yopp AC, Mansour JC, Beg MS, et al. Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome. *Ann Surg Oncol*. 2014;21(4):1287–1295. doi:10.1245/s10434-013-3413-8
110. Jia AY, Popovic A, Mohan AA, et al. Development, Practice Patterns, and Early Clinical Outcomes of a Multidisciplinary Liver Cancer Clinic. *Cancer Control*. 2021;28:10732748211009945. doi:10.1177/10732748211009945
111. Basch E, Deal AM, Dueck AC, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA*. 2017;318(2):197–198. doi:10.1001/jama.2017.7156
112. Basch E, Deal AM, Kris MG, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: a Randomized Controlled Trial. *J Clin Oncol*. 2016;34(6):557–565. doi:10.1200/JCO.2015.63.0830
113. Penrice DD, Hara KS, Sordi-Chara B, et al. Design, implementation, and impact of a cirrhosis-specific remote patient monitoring program. *Hepatol Commun*. 2024;8(8):498. doi:10.1097/HC9.0000000000000498
114. Graf J, Stengel A. Psychological Burden and Psycho-Oncological Interventions for Patients With Hepatobiliary Cancers-A Systematic Review. *Front Psychol*. 2021;12:662777. doi:10.3389/fpsyg.2021.662777
115. Asrani SK, Ghabril MS, Kuo A, et al. Quality measures in HCC care by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. *Hepatology*. 2022;75(5):1289–1299. doi:10.1002/hep.32240
116. Palmieri VO, Santovito D, Margari F, et al. Psychopathological profile and health-related quality of life (HRQOL) in patients with hepatocellular carcinoma (HCC) and cirrhosis. *Clin Exp Med*. 2015;15(1):65–72. doi:10.1007/s10238-013-0267-0
117. Fan SY, Eiser C, Ho MC, Lin CY. Health-related quality of life in patients with hepatocellular carcinoma: the mediation effects of illness perceptions and coping. *Psychooncology*. 2013;22(6):1353–1360. doi:10.1002/pon.3146
118. Chen CM, Hsu CY, Bai CH. Building a Patient Oriented Treatment Decision System for Liver Cancer. Presented at: 2012 Third Global Congress on Intelligent Systems, Wuhan, China. 2012.
119. Donlan J, Kaplan A, Noll A, et al. Prognostic Communication, Symptom Burden, Psychological Distress, and Quality of Life Among Patients with Decompensated Cirrhosis. *Clin Gastroenterol Hepatol*. 2024. doi:10.1016/j.cgh.2024.10.017
120. Ritaccio G, Barritt Iv AS, Conklin JL, et al. Scoping review of values elicitation tools for treatment decisions in hepatocellular carcinoma. *BMC Gastroenterol*. 2024;24(1):90. doi:10.1186/s12876-024-03167-1
121. Fan SY, Eiser C. Illness experience in patients with hepatocellular carcinoma: an interpretative phenomenological analysis study. *Eur J Gastroenterol Hepatol*. 2012;24(2):203–208. doi:10.1097/MEG.0b013e32834ec184
122. Norman EML, Weil J, Philip J. Hepatocellular carcinoma and its impact on quality of life: a review of the qualitative literature. *Eur J Cancer Care*. 2022;31(6):e13672. doi:10.1111/ecc.13672
123. Patel N, Maher J, Lie X, et al. Understanding the patient experience in hepatocellular carcinoma: a qualitative patient interview study. *Qual Life Res*. 2022;31(2):473–485. doi:10.1007/s11136-021-02903-4
124. Hsu WC, Tsai AC, Chan SC, Wang PM, Chung NN. Mini-nutritional assessment predicts functional status and quality of life of patients with hepatocellular carcinoma in Taiwan. *Nut Cancer*. 2012;64(4):543–549. doi:10.1080/01635581.2012.675620

125. Kuroda H, Ushio A, Miyamoto Y, et al. Effects of branched-chain amino acid-enriched nutrient for patients with hepatocellular carcinoma following radiofrequency ablation: a one-year prospective trial. *J Gastroenterol Hepatol*. 2010;25(9):1550–1555. doi:10.1111/j.1440-1746.2010.06306.x
126. Tada T, Kumada T, Toyoda H, Yasuda S, Koyabu T, Nakashima M. Impact of Branched-Chain Amino Acid Granule Therapy in Patients with Hepatocellular Carcinoma Who Have Normal Albumin Levels and Low Branched-Chain Amino Acid to Tyrosine Ratios. *Nut Cancer*. 2019;71(7):1132–1141. doi:10.1080/01635581.2019.1597905
127. Nojiri S, Fujiwara K, Shinkai N, Iio E, Joh T. Effects of branched-chain amino acid supplementation after radiofrequency ablation for hepatocellular carcinoma: a randomized trial. *Nutrition*. 2017;33:20–27. doi:10.1016/j.nut.2016.07.013
128. Hayaishi S, Chung H, Kudo M, et al. Oral branched-chain amino acid granules reduce the incidence of hepatocellular carcinoma and improve event-free survival in patients with liver cirrhosis. *Dig Dis*. 2011;29(3):326–332. doi:10.1159/000327571
129. Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Support Care Cancer*. 2008;16(7):791–801. doi:10.1007/s00520-007-0380-2
130. Firkins JL, Tarter R, Driessnack M, Hansen L. A closer look at quality of life in the hepatocellular carcinoma literature. *Qual Life Res*. 2021;30(6):1525–1535. doi:10.1007/s11136-021-02789-2