Received: 29 September 2021 | Revised: 20 December 2021 | Accepted: 20 December 2021

DOI: 10.1002/hep.32313

REVIEW

Patient-reported outcomes in HCC: A scoping review by the Practice Metrics Committee of the American Association for the Study of Liver Diseases

Marina Serper[1,2,3] | Neehar D. Parikh[4] | Grace Thiele[1] | Nadia Ovchinsky[5] | Shivang Mehta[6] | Alexander Kuo[7] | Chanda Ho[8] | Fasiha Kanwal[9,10,11] | Michael Volk[12] | Sumeet K. Asrani[13] | Marwan S. Ghabril[14] | John R. Lake[15] | Raphael B. Merriman[16] | Timothy R. Morgan[17] | Elliot B. Tapper[4,18]

[1]Division of Gastroenterology and Hepatology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[2]Section of Gastroenterology, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA

[3]Leonard Davis Institute of Health Economics, Philadelphia, Pennsylvania, USA

[4]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan, USA

[5]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Hospital at Montefiore–Albert Einstein College of Medicine, Bronx, New York, USA

[6]Hepatology, Baylor All Saints, Fort Worth, Texas, USA

[7]Division of Digestive and Liver Diseases, Cedars-Sinai Medical Center, Los Angeles, California, USA

[8]Department of Transplantation, California Pacific Medical Center, San Francisco, California, USA

[9]Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA

[10]Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA

[11]Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA

[12]Division of Gastroenterology and Transplantation Institute, Loma Linda University, Loma Linda, California, USA

[13]Hepatology, Baylor University Medical Center, Dallas, Texas, USA

[14]Indiana University School of Medicine, Indianapolis, Indiana, USA

[15]Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, Minnesota, USA

[16]California Pacific Medical Center, San Francisco, California, USA

[17]VA Long Beach Healthcare System, Long Beach, California, USA

[18]Gastroenterology Section, VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA

Correspondence
Elliot Tapper, Division of Gastroenterology and Hepatology, University of Michigan, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, USA.
Email: etapper@umich.edu

Funding information
Supported by the National Institutes of Health (1K23DK1158907-03, to M. S.; 1K23DK117055-01A1, to E. T.; and U01-CA-230669, U01-CA-230694, and 5R01CA222900, to N. P.) and by the Baylor Foundation (to S. K. A.)

Abstract

Background and Aims: HCC is a leading cause of mortality in patients with advanced liver disease and is associated with significant morbidity. Despite multiple available curative and palliative treatments, there is a lack of systematic evaluation of patient-reported outcomes (PROs) in HCC.

Approach and Results: The American Association for the Study of Liver Diseases Practice Metrics Committee conducted a scoping review of PROs in HCC from 1990 to 2021 to (1) synthesize the evidence on PROs in HCC

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D, EuroQol–5 Dimensions; FACT-Hep, Functional Assessment of Cancer Therapy, Hepatobiliary; FHSI-8, FACT Hepatobiliary Symptom Index-8; HCC-18, Hepatocellular Carcinoma-18; HRQOL, health-related quality of life; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core-30; QOL, quality of life; RFA, radiofrequency ablation; SF-12/SF-36, Short Form 12/Short Form 36; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; VAS, Visual Analogue Scale.

and (2) provide recommendations on incorporating PROs into clinical practice and quality improvement efforts. A total of 63 studies met inclusion criteria investigating factors associated with PROs, the relationship between PROs and survival, and associations between HCC therapy and PROs. Studies recruited heterogeneous populations, and most were cross-sectional. Poor PROs were associated with worse prognosis after adjusting for clinical factors and with more advanced disease stage, although some studies showed better PROs in patients with HCC compared to those with cirrhosis. Locoregional and systemic therapies were generally associated with a high symptom burden; however, some studies showed lower symptom burden for transarterial radiotherapy and radiation therapy. Qualitative studies identified additional symptoms not routinely assessed with structured questionnaires. Gaps in the literature include lack of integration of PROs into clinical care to guide HCC treatment decisions, unknown impact of HCC on caregivers, and the effect of palliative or supportive care quality of life and health outcomes.
Conclusion: Evidence supports assessment of PROs in HCC; however, clinical implementation and the impact of PRO measurement on quality of care and longitudinal outcomes need future investigation.

INTRODUCTION

HCC is the fourth most common cause of cancer death and has the second highest case-fatality rate among all cancers.[1] Treatment algorithms for HCC are complex and vary greatly in clinical settings. Depending on the cancer stage, a patient may undergo therapies that are curative (resection, ablation, liver transplantation) or palliative (locoregional, systemic, best supportive); and often, several of these therapies are used in sequence or combination. These care strategies produce diverse symptom profiles and have a variable psychosocial impact over time. In understanding the full scope of how a method of treatment will affect the outcome of a patient with HCC, it is imperative to account for the impact of a given treatment modality on patient-reported outcomes (PROs), defined as any report of the status of a patient's health condition that comes directly from the patient.[2] Multiple tools are available to assess the well-being of affected patients, however, comprehensive summaries of PROs in HCC are lacking.

Despite the significant impact of HCC and its therapies on PROs, they are rarely measured in routine clinical practice to guide treatment decisions and symptom management or inform quality improvement efforts. PROs serve at least three practical purposes. First, routine PRO collection allows systematic evaluation of where improvements are needed in patient experience, patient educational needs, and supportive care, informing navigation programs and the goals of clinical follow-up. Second, PROs may play a role in guiding decision-making regarding treatment selection and stopping rules.[3] Finally, PROs can be used to define treatment effectiveness for regulatory purposes. However, before incorporating PRO measurement into HCC care, the first step is to identify key themes of value to patients.

The American Association for the Study of Liver Diseases Practice Metrics Committee used a two-step process that includes scoping reviews and focus groups to identify candidate PROs in HCC care.[4] As previously examined for cirrhosis care,[4,5] we conducted a scoping review of the available evidence of PROs in HCC. Our overall objectives were to (1) synthesize the available evidence on PROs in HCC and (2) provide guidance on incorporating PROs into clinical practice and quality improvement efforts in HCC care. PROs and health-related quality of life (HRQOL) are often synonymous in the literature; this review will use *PROs* and *HRQOL* interchangeably.[6]

MATERIALS AND METHODS

We aimed to characterize PROs used in evaluation and management of patients with HCC. To do so, we conducted a scoping review, a variant of a systematic review that seeks to identify and map the concepts within a large body of evidence. When the body of literature is large, heterogeneous, and without a prior comprehensive review, scoping review methodology may be more appropriate than a systematic review.[7]

Search strategy

We searched four databases: PsycINFO, PubMed, Embase, and Cumulative Index to Nursing and Allied Health Literature, from inception to October 2021. The details of the search strategy applied to each database are provided in Table S1. Search terms were compiled from three major categories: names of already published PRO measures (e.g., Short Form 36 [SF-36], Functional Assessment of Cancer Therapy, Hepatobiliary [FACT-Hep], European Organisation for Research and Treatment of Cancer-Quality of Life [EORTC-QOL], EuroQoL–5 Dimensions [EQ-5D]), more general PRO terminology (e.g., *patient satisfaction*, *HRQOL*, *QOL*), and disease-specific terms (e.g., *liver cell carcinoma*, *HCC*, *hepatoma*). Studies related to bile duct carcinoma and cholangiocarcinoma were excluded. All results were compiled using the Rayyan QCRI web-based application.[8]

Study selection

Eligibility criteria

Studies were selected if they reported quantitative PRO measures provided at a granular level (at the level of domains or subscales) before or following a standard therapeutic intervention for HCC or if they provided a qualitative PRO analysis. To be included in the scoping review, studies with quantitative PRO measures had to provide sufficient details for descriptive statistics (e.g., mean, standard deviation) and information specific to HCC (e.g., studies reporting aggregate PROs of multiple malignancies were excluded). We excluded studies of children (<18 years), animals, non-English publications, case reports, abstracts, those including non-standard-of-care therapies (e.g., herbals), and those that only included patients after liver transplantation.

Review

All titles and abstracts were independently reviewed by two members of the Practice Metrics Committee for relevance. Full-text documents were then retrieved, reviewed by two reviewers, and subsequently included in the final review or excluded based on the eligibility criteria. All disagreements between reviewers were arbitrated by a third reviewer. Studies were excluded in cases of insufficient details in the methods or results if the cohorts overlapped with previously published literature. Studies validating or translating questionnaires into other languages were also excluded. Figure S1 shows the preferred reporting items for systematic reviews and meta-analyses flow diagram for study inclusion.

Data extraction and analysis

Extracted information included study design, PRO measure(s), therapeutic intervention(s), sample size, disease stage, system of cancer staging, prior therapy (if applicable), study aims, and prognostic factors (e.g., survival) identified.

Studies providing granular data from PRO measures over time were further analyzed using heat maps created in Microsoft Excel. Each study was categorized by which PRO measure(s) it reported. Baseline and longitudinal data for each subscale or domain were extracted if applicable. Longitudinal data were color-coded according to whether they demonstrated a measured improvement or deterioration and further coded according to whether that change was clinically and/or statistically significant (as reported by the individual studies). Clinical significance was determined using previously reported minimal clinically important differences for each PRO measurement. The heat map was arranged according to HCC therapy, from curative to palliative.

RESULTS

Overview

After the initial search terms and selection criteria were applied, a total of 63 articles met inclusion criteria (Figure S1). We found multiple validated questionnaires (e.g., SF-36, FACT-Hep, EORTC-QOL) used to assess multiple domains of HRQOL. HRQOL is a subset of PROs that includes social, emotional, functional, and physical well-being as well as general, liver disease–specific, and hepatobiliary cancer symptoms (Figure 1).

Physical PROs in HCC

Patients with HCC experienced a high burden of physical symptoms that were often driven by their underlying cirrhosis and liver function (Table 1). In a single center in Korea, Ryu et al. identified four major symptom clusters: (1) pain appetite, (2) fatigue-related, (3) gastrointestinal, and (4) itching-constipation.[9] High symptom burden was significantly associated with poor functional status and worse global HRQOL on the FACT-Hep scale.[10] Chung et al. found that fatigue and sleep disturbance were the most severe symptoms experienced by patients with HCC.[11] Several studies showed that the severity of the underlying liver function and tumor burden was associated with HRQOL. Li et al. found that HRQOL correlated best with indices of liver function (such as albumin and bilirubin) irrespective of tumor stage among a cohort of patients largely with Child A cirrhosis.[12] Qiao et al. found that

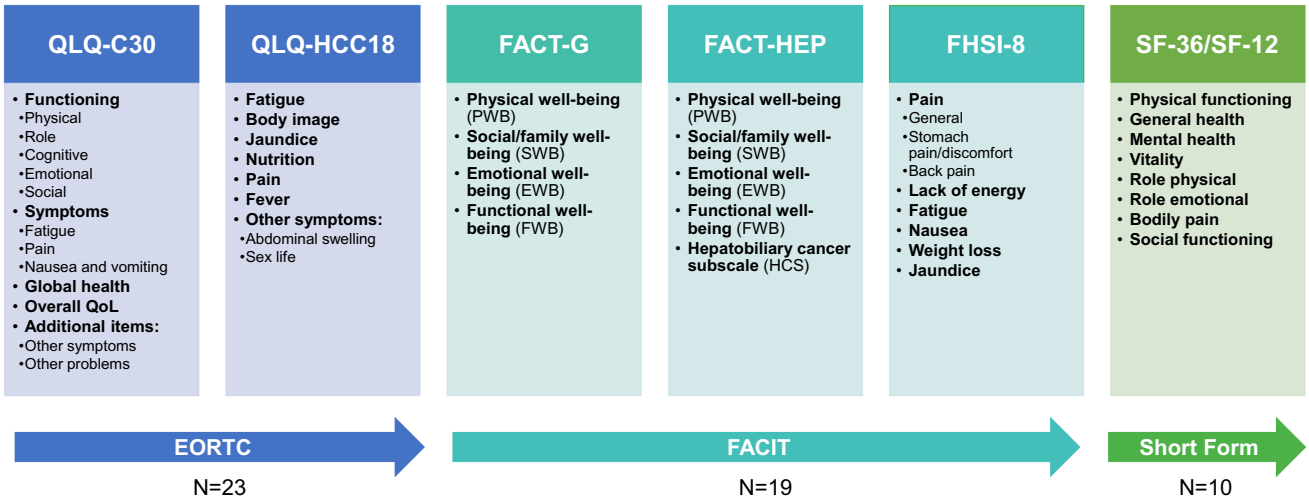

FIGURE 1 Most commonly used validated PRO questionnaires in HCC. FACIT, Functional Assessment of Chronic Illness Therapy; FACT-G, FACT–General; QLQ-HCC18, HCC-specific domain of QLQ

tumor stage was strongly and inversely associated with FACT-Hep scores, particularly for physical and emotional well-being.[13] Hsu et al. found that nutritional status was a crucial determinant of HRQOL.[14] Two studies comparing PROs among HCC and matched controls with chronic liver disease found conflicting results. Kondo et al. reported that liver disease severity (i.e., albumin level or presence of ascites), not the presence or absence of recurrent HCC, in patients treated with radiofrequency ablation (RFA) was associated with HRQOL.[15] However, Bianchi et al. found that patients with HCC reported more bodily pain and poor sleep quality compared to patients with cirrhosis.[10]

Psychosocial and psychological factors affecting PROs in HCC

Patients with HCC were found to experience a substantial burden of symptoms within psychological and social domains (Table 2). Depression and anxiety were very common[16] and became more prevalent after liver-directed therapy.[17] Hansen et al. used the Memorial Symptoms Assessment Scale to evaluate the presence, frequency, and severity of 32 symptoms among 18 patients with advanced HCC receiving palliative locoregional, systemic therapy, and radiation who were followed monthly for 6 months.[18] The most distressing symptoms were lack of energy, problems with sexual interest or activity, worrying, and feeling irritable. Fan et al. found that HCC was associated with worse global HRQOL as well as lower physical, cognitive, and social functioning but higher emotional functioning compared with population norms.[19]

In studies that compared psychosocial domains in patients with HCC to matched controls with cirrhosis, patients with HCC often reported higher levels of functioning. Steel et al. compared HRQOL in HCC prior to treatment to patients with cirrhosis without HCC and the general population using FACT-Hep. Patients with HCC reported better social and family well-being than those with cirrhosis[20] but worse sexual function and morbidity.[21] Palmieri et al. found that patients with HCC had higher scores for general health and vitality but lower scores for social functioning and role limitations than those with cirrhosis.[22] Moore et al. reported on posttraumatic growth (a concept synonymous with resilience after traumatic events) in 202 patients with HCC and did not find any changes over time or associations with HRQOL.[23]

Prognostic significance of PROs in HCC

Associations between HRQOL and survival were examined in seven studies (Table 3). Bonnetain et al.[24] pooled data from two randomized multicenter trials comparing tamoxifen with palliative care for untreatable HCC and as add-on therapy for transarterial chemoembolization (TACE). HRQOL, defined by the Spitzer QOL Index, was positively associated with survival after adjusting for tumor size, alpha-fetoprotein (AFP), and liver disease severity. Sternby Eilard et al. investigated whether the EORTC Quality of Life Questionnaire Core-30 (QLQ-C30) and Hepatocellular Carcinoma-18 (HCC-18) HRQOL questionnaires could improve prognostication of HCC survival in a prospective study of 185 previously treated patients who had residual disease.[25] Combining the HCC-18 nutrition scale with Barcelona Clinic Liver Cancer (BCLC) staging, tumor–node–metastasis stage, Eastern Cooperative Oncology Group (ECOG) performance status, and/or AFP improved survival prediction, as did adding the C30 fatigue and HCC-18 nutrition scales to the Cancer of the Liver Italian Program score.[26] In a prospective single-center study of 242 patients, Gmür et al. showed

TABLE 1 Baseline factors associated with HRQOL in HCC

References	PRO measure(s)	Cohort	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QOL
Bianchi et al.[10]	SF-36, NHP	(+): HCC	101	A (35%)	Not reported	Not reported	(+): cirrhosis	QOL in patients with cirrhosis + HCC	(+): age, male gender
				B (43%)			(+): HBV and/or HCV (75%)		(−): sleep disorders, daily medications, associated diseases, HCC diameter
				C (22%)			(+): comorbidity (64%)		
		(+): cirrhosis, (−): HCC	202	A (39%)	N/A	N/A	(+): cirrhosis		
				B (41%)			(+): HBV and/or HCV (69%)		
				C (20%)			(+): comorbidity (66%)		
Kondo et al.[15]	SF-36	(+): HCC	97	A (77%)	Not reported	(+:) PEIT or RFA	(+): recurrence (63%)	Comparison of HRQOL between patients with CLD with HCC + without HCC	(+): serum albumin, prothrombin activity
				B (21%)			(+): HBV (14%)		(-): age (PCS), female sex (PCS), presence of ascites (PCS), platelet count
				C (2%)			(+): HCV (84%)		
		(+): CLD, (−): HCC	97	A (89%)	N/A	N/A	(+): HBV (10%)		
				B (11%)			(+): HCV (88%)		
Hsu et al.[14]	EORTC QLQ- C30	N/A	300	A (67%)	AJCC I (7%), II (34%), III (42%), IV (16%)	Not reported	(+): HBV (54%)	QOL evaluation using nutrition-based instrument	(+): nutritional status, hemoglobin, albumin, self-rated health status, motility
				B (29%)			(+): HCV (51%)		(−): tumor staging, CTP score, WBC
				C (3%)					
Li et al.[12]	EORTC QLQ-C30 and HCC-18	N/A	517	A (67%)	Not reported	None	(+): cirrhosis (59%)	Correlation between baseline QOL + liver function	(+): albumin, albumin-to-ALP ratio
				B (28%)			(+): HBV (82%)		(-): ALBI grade, ascites, MELD,
				C (5%)			(+): HCV (6%)		

(Continues)

TABLE 1 (Continued)

References	PRO measure(s)	Cohort	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QOL
Steel et al.[20]	FACT-Hep	(+): HCC	83	A (51%) B (26%) C (1%)	TNM I and II (20%), III and IV (80%)	None	(+): HBV (9%) (+): HCV (30%)	HRQOL comparison between HCC, CLD, and general population	N/A
		(+): CLD, (−): HCC	51	A (60%) B (30%) C (10%)	N/A	None	(+): HBV (4%) (+): HCV (43%)		
Ryu et al.[9]	FACT-Hep, HADS, Korean HCC symptom checklist	(+): HCC	180	A (83%) B (16%) C (1%)	9% with metastatic disease	Not reported	(+): HBV (81%) (+): HCV (11%)	Identify symptom clusters; association between symptom clusters and HRQOL	(+): anxiety, depression
Qiao et al.[13]	FACT-Hep	N/A	140	A (60%) B (21%) C (19%)	TNM I (35%), II (25%), IIIA (21%), IIIB (19%)	None	(+): cirrhosis (+): HBV (97%) (+): HCV (1%)	QOL changes by TNM staging	(−): TNM stage
Chung et al.[11]	MDASI-T	N/A	100	A (48%) B (33%) C (19%)	TNM I (16%), II (31%), III (45%), IV (8%)	RT (30%) TAE (29%) PEIT (24%)	(+): metastasis (92%)	Symptom cluster analysis; impact of sleep/fatigue on symptoms	(−): fatigue, sleep disturbance

Abbreviations: AJCC, American Joint Committee on Cancer Staging; ALBI, albumin-bilirubin grade; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CLD, chronic liver disease; CRP, C-reactive protein; CTP, Child-Turcotte-Pugh (score or class); GGT, gamma-glutamyl transpeptidase; HADS, Hospital Anxiety and Depression Scale; PCS, physical component score (SF); INR, international normalized ratio; MDASI-T, MD Anderson Symptom Inventory (Taiwanese version); MELD, Model for End-Stage Liver Disease; N/A, not available; NHP, Nottingham Health Profile; PEIT, percutaneous ethanol injection therapy; RT, radiation therapy; TAE, transarterial embolization; TNM, tumor–node–metastasis; WBC, white blood cells.

TABLE 2 Psychosocial and psychological factors associated with HRQOL in HCC

References	PRO measure(s)	Cohort	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QOL
Palmieri et al.[22]	SF-36, SCL-90-R, TAS-20, Hamilton-D	(+): cirrhosis	22	A (91%) B (9%)	N/A	Not reported	(+): HBV (27%) (+): HCV (64%)	Development of behavioral + psychopathological profile of HCC, association with prognostics + QOL	(−): depression, somatization, anxiety
		(+): HCC	24	A (88%) B (12%)	BCLC A (71%), B (17%), D (13%)	Not reported	(+): HBV (17%) (+) HCV (79%)		(−): depression, somatization,
Fan et al. [19]	EORTC QLQ-C30	N/A	286	A (78%) B (15%) C (6%)	AJCC 1 (38%), 2 (23%), 3 (30%), 4 (4%)	HR (41%), TACE/TAE (34%), chemotherapy (26%)		Characterization of QOL in HCC, physical + psychological predictors of QOL	(+): problem-oriented coping, understanding, emotional functioning, physical functioning; (−): ECOG PS, AFP levels, negative
Mikoshiba et al.[16]	EORTC QLQ-C30 and HCC-18	N/A	128	A (76%) B and C (24%)	Not reported	Curative treatment	(+): HBV (34%) (+): HCV (59%) (+): comorbidity (65%)	Association of depressive symptoms + QOL, characterization in HCC survivors	QOL: (−): depressive symptoms Depressive symptoms: (+): KPS; (−): CTP score, living alone, unemployment
Steel et al.[21]	FACT-Hep, sexual history questionnaire	(+): HCC	21	A (73%) B (18%)	TNM III (5%), IV (95%)	Not reported	Entirely men (+): cirrhosis (84%) (+): HBV (13%) (+): HCV (44%)	Evaluation of sexual morbidities in HCC population	(−): sexual problems
		(+): CLD	23	A (67%) B (27%) C (6%)	N/A		Entirely men (+): cirrhosis (88%) (+): HCV (57%)		
Moore et al.[23]	FACT-Hep, CES-D, PTG	(+): hepatobiliary malignancy	202, 67% +HCC	Not reported	Not reported	Chemotherapy (70%), surgery (14%), combination (8%), no treatment (8%)	(+): cirrhosis (78%)	Association of PTG and HRQOL, depressive symptoms	No associations between PTG and HRQOL

(Continues)

TABLE 2 (Continued)

References	PRO measure(s)	Cohort	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QOL
Lee et al.[17]	FACT-Hep, BAI, BDI	N/A	410	Not reported	TNM I (57%), II (27%), III&IV (16%)	Chemotherapy (3%) Radiotherapy (1%)	(+): cirrhosis (40%) (+) HBV (28%) (+) HCV (16%)	Longitudinal effects of anxiety + depression in patients with HCC following resection	(−): anxiety, depression
Hansen et al.[18]	MSAS	(+): HCC	18	Not reported	Not reported	Not reported	(+): HBV (6%) (+): HCV (61%)	Longitudinal assessment of symptom distress in advanced HCC population	N/A

Abbreviations: AJCC, American Joint Committee on Cancer Staging; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies Depression Scale; CLD, chronic liver disease; CTP, Child-Turcotte-Pugh (score or class); Hamilton-D, Hamilton Depression rating scale; HR, hepatic resection; KPS, Karnofsky performance score; MSAS, Memorial Symptom Assessment Scale; N/A, not available; PS, performance status; PTG, post-traumatic growth; SCL-90-R, Symptom Checklist 90-R; TAE, transarterial embolization; TAS-20, Toronto Alexithymia Scale; TNM, tumor–node–metastasis.

TABLE 3 HRQOL as a prognostic factor in HCC

References	PRO measure(s)	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Proposed prognostic factors for survival
Meier et al.[31]	EORTC QLQ-C30 and HCC-18	130	A (43%) B (35%) C (22%)	BCLC A (40%), B (17%), C (20%), D (23%)	None	(+): stage 4 cirrhosis (+): HCV (73%)	Prognostication of survival with QOL data	(+): role functioning, Caucasian race, receipt of HCC treatment (−): BCLC stage
Sternby Eilard et al.[25]	EORTC QLQ-C30 and HCC-18	185	A (70%) B (27%) C (3%)	BCLC 0 (3%), A (22%), B (22%), C (47%), D (6%); TNM I (26%), II (27%), III (47%)	Not reported, mostly treatment-naive	(+): cirrhosis (74%) (+): HCV (50%) (+): HBV (8%) (+): comorbidity (58%)	Improvement of prognostication of survival with QOL	(+): physical functioning (−): fatigue, nutrition, BCLC stage, CLIP stage, CTP score, TNM stage, AFP
Li et al.[28]	EORTC QLQ-C30 and HCC-18	517	A (68%) B (28%) C (4%)	Not reported	None	(+): cirrhosis (59%) (+): HBV (82%) (+): HCV (6%)	Prognostication of survival with QOL index score	(+): physical functioning, HCC-18 index score, C30 index score, albumin (−): pain, fatigue, metastases, multifocal or diffuse HCC,
Kim et al.[29]	EORTC QLQ-C30 and HCC-18	300	A (91%) B (9%)	BCLC 0 (12%), A (34%), B (22%), C (32%) TNM I (32%), II (22%), III (37%), IV (9%)	Surgery (4%), local ablation (2%), embolization (21%), sorafenib (2%), combined therapy (10%)	(+): cirrhosis (73%)	Prognostication of survival with QOL	(−): role functioning, appetite loss
Gmür et al.[27]	FACT-Hep	242	A (67%) B (29%) C (4%)	BCLC 0 (5%), A (36%), B (35%), C (18%), D (6%)	TACE (35%), HR (22%), LT (10%), SIRT (9%), ablation (5%), sorafenib (12%), palliative (6%)	(+): cirrhosis (82%) (+): HBV (30%) (+): HCV (21%)	Prognostication of survival with QOL + ECOG PS	(+): functional, emotional, and physical well-being, HBS, FACT-G, FACT-Hep (−): ECOG PS
Deng et al.[30]	SF-12	735	A (79.5%)	TNM III and IV (70.6%)	Yes (26.1%)	(+): HCV and/or HBV (25.3%)	Prognostication of survival with QOL	Survival: (−): low to medium PCS, low MCS PCS: (+): high LMR; (−): smoking status, CTP score, high ALP MCS: (+): older age, high LMR; (−): high direct bilirubin Both components: (−): abnormal WBC counts, high NLR, low albumin

(Continues)

TABLE 3 (Continued)

References	PRO measure(s)	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Proposed prognostic factors for survival
Bonnetain et al.[24]	Spitzer QOL index	538	A (57%) B (40%) C (3%)	BCLC A (3%), B (13%), C (76%), D (8%); Okuda 1 (41%), 2 (52%), 3 (7%)	Not reported	Palliative HCC (+): cirrhosis (93%)	Improvement of prognostication with QøL	(+): Spitzer score, albumin, small HCC (−): jaundice, hepatomegaly, hepatalgia, ascites, PVT,

Abbreviations: ALP, alkaline phosphatase; CLIP, Cancer of the Liver Italian Program staging; CTP, Child-Turcotte-Pugh (score); FACT-G, FACT-General; HBS, hepatobiliary subscale; HR, hepatic resection; LMR, lymphocytes-to-monocytes ratio; LT, liver transplantation; MCS, mental component score; NLR, neutrophils-to-lymphocyte ratio; PCS, physical component score; PS, performance status; PVT, portal vein thrombosis; SIRT, selective internal radiation therapy; TNM, tumor–node–metastasis; WBC, white blood cells.

that the FACT-Hep questionnaire improves prognostication beyond ECOG performance status.[27] Li et al. investigated the prognostic significance of QLQ-C30, QLQ-HCC-18, and C30/HCC-18 index scores in patients with newly diagnosed HCC of various stages.[28] A higher symptom burden on the QLQ-C30 index and the QLQ-HCC-18 was associated with higher adjusted mortality. Kim et al. evaluated EORTC QLQ-30, QLQ-HCC-18, and FACT-Hep in a Korean cohort of 300 patients and found that EORTC role functioning and the hepatobiliary cancer subscale of the FACT-Hep enhanced the prediction of 1-year survival when added to conventional cancer staging systems (American Joint Committee on Cancer and BCLC). The role functioning and appetite loss subscales in the EORTC QLQ-C30 were associated with disease progression and 1-year survival in multivariable analysis.[29] In a cohort of 735 patients with HCC, Deng et al. found that female sex, Black race, current tobacco use, and comorbidities were associated with poor physical and/or mental HRQOL on the Short Form 12 (SF-12). Patients with low or medium physical component scores compared to high scores had lower adjusted survival.[30] Meier et al. prospectively evaluated the HRQOL of 130 patients with treatment-naive HCC using the QLQ-C30 and the QLQ-HCC-18 and found that in addition to BCLC stage and HCC-directed treatment, a domain of HRQOL called *role function* (e.g., ability to perform daily activities, leisure-time activities, and work) was associated with survival.[31] In sum, although underlying disease severity often accounted for differences in PROs in cross-sectional studies, PROs improved predictions of mortality when added to medical factors.

Qualitative studies of PROs in HCC

We found seven qualitative studies. The dominant themes elicited are summarized in Figure 2. Gill et al. conducted an online survey with open-ended questions among 256 patients with HCC in 13 countries, 50% of whom underwent resection or transplant.[32] Respondents were asked for three words that best described their feelings regarding HCC on diagnosis. The five most common words were *fear*, *worry*, *scared*, *anxiety*, and *shock*. Respondents reported worsened concentration (47%), physical condition (44%), and mental condition (36%). Of all treatment modalities (liver-directed and systemic, excluding surgery), 37% reported TACE and 25% reported sorafenib to be the most challenging therapies. Overall, 60% reported permanently stopping work due to side effects. Fan and Eiser conducted 33 semistructured interviews among patients at various HCC stages treated with resection, TACE, and systemic therapy. Patients endorsed physical symptoms (weakness, anorexia, flatulence) and psychosocial stress (depression, poor sleep, worry, fear

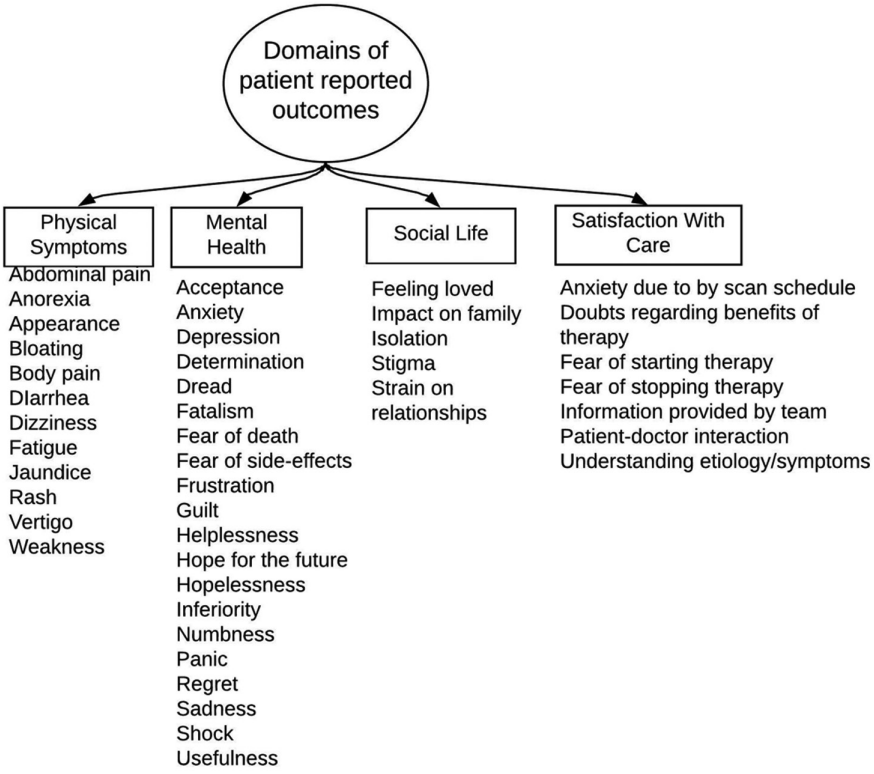

FIGURE 2 Dominant themes elicited in qualitative studies

of death) as well as some positive changes (more focus on self-care). Patients reported social strain: inability to work, dependence, and adding stress to family with respect to uncertainties regarding the results of upcoming imaging tests or changes in the treatment plan.[33] Hansen et al. prospectively evaluated HCC symptoms among 14 patients with HCC beyond Milan criteria for up to 6 months.[34] Major themes elicited were hope and hopelessness (even in the same patient) and fear in anticipation of liver scans. Patients reported distress caused by limited knowledge of the prognosis, HCC etiology, and treatment options including transplant. Not having transplant as an option was painful for some and relieving for others. Some expressed regret over treatment and severe dislike of sorafenib. Kaiser et al. conducted 10 semistructured interviews of patients with HCC treated with sorafenib and found that gastrointestinal symptoms (diarrhea, abdominal pain, bloating, anorexia, nausea) were the most common and important to the patients, followed by fatigue and skin toxicity.[35] Lo et al. conducted a stated preference study with 150 European patients with HCC to determine their perspectives on therapy.[36] Patients preferred one-time therapies and oral therapies to infusions. Overall survival benefits were the most important predictor of treatment selection; however, patients would trade survival time to reduce the risk of hypertension, gastrointestinal effects, and fatigue. Lee[37] elicited negative themes (depressive symptoms and spiritual distress) and positive themes (acceptance, connectedness to someone/thing, satisfaction with and meaningfulness in life). The main subthemes were exhaustion, regret, stigma, sadness, anger, fear, anguish, nervousness, pain, helplessness, ambivalence, hopelessness, irritability, frustration, neglect, guilt, being punished by God, and abandonment. Patel et al. found in interviews with 25 patients with BCLC stages that the most prevalent and disturbing experiences were fatigue, frustration, fear, and depression.[38] Abdominal pain and skin complaints were common and disturbing for BCLC-C patients.

Effects of HCC therapy on PROs—registration trials

PROs have been assessed in several clinical trials of unresectable HCC (Table 4). In IMBRAVE150, atezolizumab–bevacizumab was associated with a reduced risk of deterioration on all QLQ-C30 generic cancer symptom scales (appetite loss, diarrhea, fatigue, pain) and several QLQ-HCC-18 disease-specific symptom scales (fatigue, pain) when compared to sorafenib. Atezolizumab–bevacizumab versus sorafenib was associated with delayed deterioration of global HRQOL (11.2 vs. 3.6 months), physical functioning (13.1 vs. 4.9 months), and role functioning (9.1 vs. 3.6 months).[39,40] In the Phase 3 REFLECT trial (lenvatinib vs. sorafenib), baseline HRQOL scores were similar and declined in both groups following initiation of treatment. Time to

TABLE 4 Effects of HCC therapy on HRQOL

References	PRO measure(s)	Therapy	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QoL
Registration trials									
Vilgrain et al.[47]	EORTC QLQ-C30 + HCC-18	TARE/SIRT	237	A (83%) B (16%)	BCLC A (4%), B (28%), C (68%)	TACE (45%)	(+): cirrhosis (89%) (+): HBV (5%) (+) HCV (23%)	Safety and efficacy comparison between sorafenib and SIRT with Y90 microspheres	N/A
		Sorafenib	222	A (84%) B (16%)	BCLC A (5%), B (27%), C (67%)	TACE (42%)	(+): cirrhosis (91%) (+): HBV (7%) (+): HCV (22%)		N/A
Kudo et al.[41]	EORTC QLQ-C30 + HCC-18	Lenvatinib	478	A (99.4%) B (0.6%)	BCLC B (21.8%), C (78.2%)	Yes (68.4%)	(+): cirrhosis (74.5%) (+): HBV (52.5%) (+): HCV (19.0%)	Survival comparison between lenvatinib and sorafenib	(+): AFP levels
		Sorafenib	476	A (98.9%) B (1.1%)	BCLC B (19.3%), C (80.7%)	Yes (72.3%)	(+): cirrhosis (76.5%) (+): HBV (47.9%) (+): HCV (26.5%)		(+): AFP levels
Finn et al.[39]	EORTC QLQ-C30	Atezolizumab + bevacizumab	336	A5 (72%) A6 (28%)	BCLC A (2%), B (15%), C (82%)	Local therapy (48%)	(+): HBV (49%) (+): HCV (21%), nonviral etiology (30%)	Safety and efficacy of atezolizumab + bevacizumab	N/A
		Sorafenib	165	A5 (73%) A6 (27%)	BCLC A (4%), B (16%), C (81%)	Local therapy (52%)	(+): HBV (46%) (+): HCV (22%), nonviral etiology (32%)		N/A
Vogel et al.[42]	EORTC QLQ-C30 + HCC-18	Lenvatinib	478	A (99.4%) B (0.6%)	BCLC B (21.8%), C (78.2%)	Yes (68.4%)	(+): cirrhosis (74.5%) (+): HBV (52.5%) (+): HCV (19.0%)	HRQOL comparison between lenvatinib and sorafenib	(+): responders
		Sorafenib	476	A (98.9%) B (1.1%)	BCLC B (19.3%), C (80.7%)	Yes (72.3%)	(+): cirrhosis (76.5%) (+): HBV (47.9%) (+): HCV (26.5%)		(+): responders
Galle et al.[40]	EORTC QLQ-C30 + HCC-18	Atezolizumab + bevacizumab	336	Not reported	Not reported	Treatment-naive		HRQOL comparison between atezolizumab + bevaciumab and sorafenib	N/A
		Sorafenib	165	Not reported	Not reported				N/A

TABLE 4 (Continued)

References	PRO measure(s)	Therapy	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QoL
Ryoo et al.[46]	EORTC QLQ-C30 + HCC-18	Pembrolizumab	271	A5 (63.3%) A6 (36.3%) B (0.4%)	BCLC B (20.1%), C (79.9%)	Prior sorafenib therapy	(+): HBV (25.9%) (+): HCV (15.5%)	Longitudinal HRQOL comparison between pembrolizumab and PBO	N/A
		PBO	127	A5 (63.7%) A6 (34.8%) B (1.5%)	BCLC B (21.5%), C (78.5%)		(+): HCV (21.5%) (+): HCV (15.6%)		N/A
Chau et al.[59]	FHSI-8 EQ-5D EQ-5D-VAS	Ramucirumab (ITT)	283	A (98%) B and C (2%)	BCLC B (12%), C (88%)	Prior sorafenib therapy	(+): HCV (27.2%) (+): HBV (27.3%)	HRQOL + PS evaluation after ramucirumab therapy	N/A
		PBO (ITT)	282	A (98%) B and C (2%)	BCLC B (12%), C (88%)		(+): HCV (35.3%) (+): HBV (35.8%)		N/A
Zhu et al.[44]	FHSI-8 EQ-5D	Ramucirumab	316	A (60.1%)	BCLC B (14.2%), C (85.8%)	Prior sorafenib therapy	(+): HBV (39.2%) (+): HCV (26.3%)	HRQOL evaluation for ramucirumab therapy	N/A
		PBO	226	A (59.7%)	BCLC B (12.8%), C (87.2%)		(+): HBV (45.1%) (+): HCV (24.8%)		N/A
Kudo et al.[43]	FHSI-8	Ramucirumab	316	A (60.1%)	BCLC B (14.2%), C (85.8%)	Prior sorafenib therapy	(+): HBV (39.2%) (+): HCV (26.3%)	Evaluation of safety and efficacy of ramucirumab	N/A
		PBO	226	A (59.7%)	BCLC B (12.8%), C (87.2%)		(+): HBV (45.1%) (+): HCV (24.8%)		N/A
Chow et al.[48]	EQ-5D	SIRT	182	A (90.7%) B (7.7%)	BCLC A (0%), B (51.1%), C (48.4%)	Not reported	(+): HBV (51.1%) (+): HCV (14.3%) (+): HBV + HCV (2.2%)	Evaluation of safety and efficacy of SIRT and sorafenib	N/A
		Sorafenib	178	A (89.9%) B (9.0%)	BCLC A (0.6%), B (54.5%), C (44.9%)	Not reported	(+): HBV (56.4%) (+): HCV (10.7%) (+): HBV + HCV (2.8%)		N/A

(Continues)

TABLE 4 (Continued)

References	PRO measure(s)	Therapy	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QoL
Yau et al.[45]	EQ-5D-3L	NV (1 mg/kg) + IP (3 mg/kg) every 3 weeks, then NV (240 mg) every 2 weeks	50	A (100%)	BCLC 0 (2%), A (4%), B (8%), C (86%)	Prior sorafenib therapy	(+): HBV (56%) (+): HCV (14%)	Evaluation of safety and efficacy of NV + IP in advanced HCC	N/A
		NV (3 mg/kg) + IP (1 mg/kg) every 3 weeks, then NV (240 mg) every 2 weeks	49	A (96%)	BCLC 0 (0%), A (0%), B (8%), C (92%)		(+): HBV (43%) (+): HCV (29%)		N/A
		NV (3 mg/kg) every 2 weeks	49	A (96%)	BCLC 0 (0%), A (0%), B (6%), C		(+): HBV (53%) (+): HCV (24%)		N/A
Real-world evidence									
Shomura et al.[65]	SF-36	Sorafenib	54	A (76%)	TNM III (43%), IV (57%)	Yes (91%)	(+): HCV (44%)	Longitudinal HRQOL after sorafenib, prognostic factors	(+): previous curative therapy, physical and social functioning
				B (24%)			(+): HBV (20%)		(−): vascular invasion, CTP, DCP
Chiu et al.[63]	SF-36 FACT-Hep	Resection	369	Not reported	TNM I (59%), II (28%), III (14%)	Yes (4%)		HRQOL after resection, domain MCIDs, prognostic factors	(+): education level, BMI, HRQOL subscale score; (−): comorbidities
Wible et al.[62]	SF-36	TACE	73	A (47%) B (51%) C (3%)	Okuda 1 (55%), 2 (42%), 3 (3%)	None		Longitudinal HRQOL after first TACE	N/A
He et al.[64]	SF-36	Transplant	22	A (27%) B (36%) C (36%)	Not reported	None	(+): HBV (82%)	HRQOL comparison between transplant, resection, and RFA	N/A
		Resection	68	A (88%) B (12%)			(+): HBV (87%)		N/A
		RFA	38	A (47%) B (50%) C (3%)			(+): HBV (82%)		N/A

TABLE 4 (Continued)

References	PRO measure(s)	Therapy	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QoL
Shun et al.[66]	SF-12 SDS, HADS	TACE	89	A (90%) B (10%)	BCLC A (46%), B (47%), C (7%)	Yes (69%)	(+): HCV (39%) (+): HBV (63%)	Longitudinal HRQOL after first TACE, prognostic factors	PCS: (+): age, recurrent disease MCS: (−): male, recurrent disease
Iwata et al.[72]	EORTC QLQ-C30 and HCC-18 SF-36	IGPT	71	A5 (69%) A6 (21%) B (10%)	BCLC 0 (10%), A (63%), B (2%), C (21%), D (4%) TNM I (82%), II (15%), III (3%);	Yes (35%)	(+): HBV (10%) (+): HCV (39%)	Safety and efficacy of IGPT in elderly cohort	(+): female sex, primary tumor (−): ECOG PS, CTP score, high
Lee et al.[61]	EORTC QLQ-C30, WHOQOL-BREF, VAS	Resection	161	A (93%) B (5%) C (2%)	Not reported	Not reported	(+): HCV (42%) (+): HBV (64%) (+): cirrhosis (57%)	Longitudinal HRQOL and survival	(+): resection
Chie et al.[56]	EORTC QLQ-C30 + HCC-18	Resection	53	A (92%) B and C (8%)	BCLC A (91%), B&C (9%)	Yes (28%)	(+): cirrhosis (64%) (+): comorbidity (51%)	Longitudinal HRQOL comparison between resection + RFA + TACE; domain MIDs	N/A
		RFA	53	A (70%) B and C (30%)	BCLC A (58%), B&C (42%)	Yes (70%)	(+): cirrhosis (81%) (+): comorbidity (79%)		N/A
		TACE	65	A (75%) B and C (25%)	BCLC A (37%), B and C (63%)	Yes (69%)	(+): cirrhosis (68%) (+): comorbidity (60%)		N/A
Hinrichs et al.[57]	EORTC QLQ-C30 + HCC-18	TACE	79	A (76%) B (19%)	Not reported	None		HRQOL after first TACE, prognostic factors	(+): symptom score (−): MELD, CTP, ECOG PS, GHS, and functional scores
Hartrumpf et al.[58]	EORTC QLQ-C30 + HCC-18	TACE	148	A (74%) B and C (26%)	Not reported	None	(+): HCV (30%) (+): HBV (18%)	HRQOL after repetitive TACE, prognostic factors	(+): symptom score (−): GHS and functional scores
Kirchner et al.[71]	EORTC QLQ-C30 + HCC-18	TACE	47	A (78.3%) B (21.7%)	Not reported	Treatment-naive	(+): cirrhosis (56.5%) (+): HBV (4.3%) (+): HCV (17.4%)	HRQOL comparison between TACE and TARE for unresectable HCC	(+): less fever (−): female sex
		TARE	27	A (85.7%) B (14.3%)	Not reported	Treatment-naive	(+): cirrhosis (47.6%) (+): HBV (9.5%) (+): HCV (14.3%)		(−): female sex, higher age

(Continues)

TABLE 4 (Continued)

References	PRO measure(s)	Therapy	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QoL
Hassanin et al.[67]	EORTC QLQ-C30 + HCC-18	TACE	45	A (26.6%) B (60%) C (13.4%)	All BCLC B	Not reported	Post-HCV (64%) HCV + HBV (3%)	HRQOL comparison between TACE and TACE + RFA	N/A
		TACE + RFA	28	A (22.4%) B (64.3%) C (14.3%)	All BCLC B	Not reported			N/A
Pereira et al.[69]	EORTC QLQ-C30	TARE	122	A5+6 (86%) B (13%)	BCLC A (4%), B (31%), C (65%)	TACE (53%)	(+): cirrhosis (89.3%) (+): HBV (3.3%) (+): HCV (18.0%)	HRQOL comparison between TARE and sorafenib	(+): low tumor burden
		Sorafenib	136	A5 + A6 (91%) B (9%)	BCLC A (4%), B (26%), C (69%)	TACE (45%)	(+): cirrhosis (90.2%) (+): HBV (4.9%) (+): HCV (21.5%)		(+): low tumor burden
Loffroy et al.[68]	EORTC QLQ-C30 + HCC-18	TARE + SIR	200 (114 HCC)	Not reported	Not reported	Yes (54.5%)	(+): cirrhosis (71%) (+): HBV 2.5%) (+): HCV (23.5%)	Evaluation of safety and HRQOL after TARE with Y90 microspheres	N/A
Brunocilla et al.[49]	FACT-Hep FHSI-8	Sorafenib	36	A (100%)	BCLC B (8%), C (92%)	Yes (69%)	(+): cirrhosis (92%) (+): HCV (47%) (+): HBV (11%)	Feasibility of sorafenib during 2-month treatment	N/A
Salem et al.[50]	FACT-Hep	TARE (Y-90)	29	A (86%) B (14%)	BCLC A (21%), B (41%), C (38%) UNOS T1–3 (41%), T4a+ (59%)	None		HRQOL comparison between TARE + TACE	N/A
		TACE	27	A (85%) B (15%)	BCLC A (56%), B (30%), C (14%); UNOS T1–3 (74%), T4a+ (26%)				N/A
Poon et al.[51]	FACT-G	Resection	66	A (94%) B and C (6%)	TNM I (3%), II (44%), III (47%), IV (6%)	Yes (69%)	(+): cirrhosis (41%) (+): comorbidity (27%)	Longitudinal HRQOL evaluation after resection	(−): TNM staging, recurrent disease
		TACE	10	Not reported	Not reported	Not reported	Inoperable HCC		N/A

TABLE 4 (Continued)

References	PRO measure(s)	Therapy	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QoL
Huang et al.[52]	FACT-Hep	RFA	121	Not reported	BCLC A	None	(+): HBV (+): cirrhosis (79%) (+): comorbidity (23%)	Longitudinal HRQOL + survival comparison between resection + RFA	(+): antiviral treatment (−): cirrhosis, comorbidities
		Resection	225				(+): HBV (+): cirrhosis (88%) (+) co-morbidity (18%)		
Wang et al.[53]	FACT-G	TACE	40	A (80%) B (20%)	TNM I and II (48%), III (13%), IV (40%)	None	(+): comorbidity (73%)	HRQOL comparison between TACE alone and TACE + RFA	(+) income; (−): recurrent disease, posttreatment CTP
		TACE + RFA	43	A (79%) B (21%)	TNM I and II (49%), III (7%), IV (44%)	None	(+): comorbidity (56%)		(+): age (−): recurrent disease, posttreatment CTP
Toro et al.[54]	FACT-Hep	Resection	14	A (100%)	Not reported	Not reported	(+): HCV (93%) (+): HBV (7%)	Longitudinal HRQOL comparison for various HCC therapies	N/A
		TACE	15	A (60%) B (40%)			(+): HCV (87%) (+): HBV (13%)		N/A
		RFA	9	A (22%) B (78%)			(+): HCV		N/A
		Best supportive care	13	A (23%) B (77%)			(+): HCV (92%) (+): HBV (8%)		N/A
Liu et al.[55]	FACT-Hep	Resection + thrombectomy	65	A and B (76%) C (24%)	BCLC C	Not reported		Comparison of outcomes, survival, and HRQOL between HR + thrombectomy and chemotherapy	N/A
		Chemotherapy	50	A and B (75.4%) C (24.6%)					
Salem et al.[70]	FHSI-8 with 7 questions from FACT-Hep	TARE (Y-90)	40	Not reported	Not reported	Not reported		Efficacy of an automated digital patient engagement platform	N/A

(Continues)

TABLE 4 (Continued)

References	PRO measure(s)	Therapy	Sample size	CTP class	Staging	Prior therapy?	Other notes	Aims	Prognostic factors for survival and/or changes in QoL
Cao et al.[60]	MDASI	TACE	155	A (94%) B (6%)	BCLC A (27%), B (41%), C (32%)	None		Cross-sectional symptom PCA after first TACE	N/A

Abbreviations: BMI, body mass index; CTP, Child-Turcotte-Pugh (score); DCP, des-gamma carboxyprothrombin; EQ-5d-3L, three-level version of EQ-5D; FACT-G, FACT-General; GHS, global health status; HADS, Hospital Anxiety and Depression Scale; HR, hepatic resection; IGPT, image-guided proton therapy; IP, ipillumumab; ITT, intention to treat; MCID, minimal clinically important difference; MCS, Mental Component Summary (score); MDASI, MD Anderson Symptom Inventory; MELD, Model for End-Stage Liver Disease; MID, minimally important difference; N/A, not available; NV, nivolumab; PBO, placebo; PCA, principal component analysis; PCS, Physical Component Summary (score); PIVKA-II, protein-induced by vitamin K absence or antagonist-II; PS, performance status; SDS, Symptom Distress Scale; SIR, systemic inflammatory response; SIRT, selective internal radiation therapy; TNM, tumor–node–metastasis; UNOS, United Network for Organ Sharing T staging; WHOQOL-BREF, World Health Organization Quality of Life Instrument, Short Form.

clinically meaningful deterioration in role functioning, pain, and diarrhea (QLQ-C30), nutrition, and body image (QLQ-HCC-18), and EQ-5D Visual Analogue Scale (VAS) was nominally shorter with sorafenib compared to lenvatinib.[41,42]

HRQOL has been evaluated for ramucirumab, nivolumab and ipilumimab, and pembrolizumab. In the Phase 3 REACH-2 study, ramucirumab was compared to placebo in patients with unresectable HCC who had received first-line therapy. The median time to deterioration in FACT Hepatobiliary Symptom Index-8 (FHSI-8) total score was prolonged with ramucirumab (3.3 vs. 1.9 months).Time to deterioration in EQ-5D score was not significantly different between ramucirumab and placebo.[43,44] In the Phase 2 study comparing three different doses of nivolumab and ipilimumab for unresectable HCC in the second-line setting, the high-dose arms with the most efficacious effect on progression-free survival resulted in superior HRQOL compared to lower doses based on EQ-5D VAS and utility index.[45] In the Phase 3 KEYNOTE-240 study (pembrolizumab vs. placebo), from baseline to week 12 changes in both EORTC QLQ-C30 and QLQ-HCC-18 scores and time to deterioration were similar for both arms.[46]

Two Phase 3 trials have evaluated radioembolization versus sorafenib for the treatment of unresectable HCC. In the SARAH trial, the global health status subscore was significantly better in the radioembolization (Y90) group than in the group with sorafenib.[47] In the SIRVENIB trial, there were no significant differences in the EQ-5D index between the radioembolization and sorafenib groups throughout the study in either the intention-to-treat or per-protocol populations; however, radioembolization had fewer Grade 3 or higher adverse events.[48]

Effects of HCC therapy on PROs—real-world evidence

The longitudinal changes in PROs associated with therapy in real-world settings are detailed in Figures 3 and 4 and Table 4.[49–72] Studies were heterogeneous with respect to eligibility criteria, methods for tumor staging, PRO measures, timing of assessments, and duration of follow-up. However, generally, hepatic resection and ablative therapies (e.g., curative) were associated with clinically significant symptom improvement, although there was some heterogeneity across studies (minimally important differences are shown in Figure 3). In the Functional Assessment of Chronic Illness Therapy questionnaire (Figure 3), locoregional therapy (largely TACE) was generally associated with symptom deteriorations, as were sorafenib and best supportive care. When assessed with SF-12, SF-36, and EORTC QLQ instruments (Figure 4A), curative therapies, TACE,

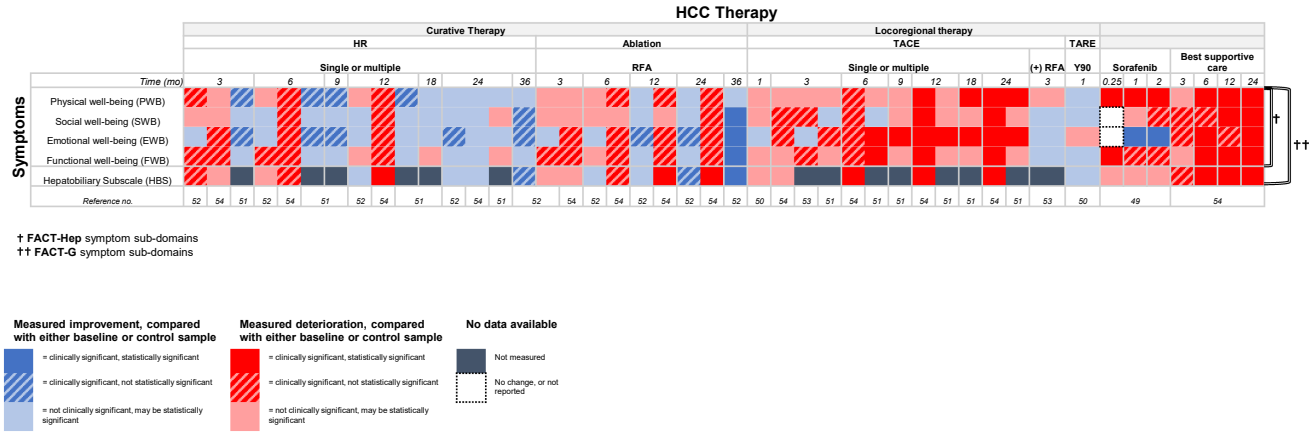

FIGURE 3 Changes in HRQOL over time in patients with HCC undergoing various treatment methods compared with baseline as Functional Assessment of Chronic Illness Therapy. FACT-G, FACT–General; HR, hepatic resection; Y90, 90-yttrium

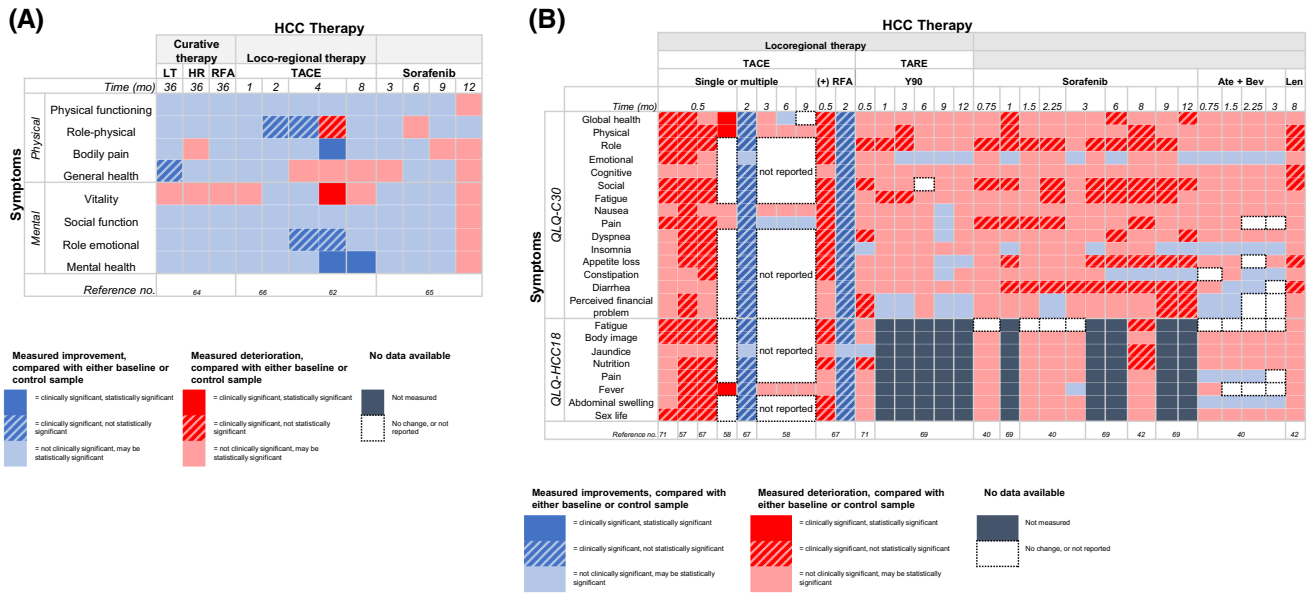

FIGURE 4 Changes in HRQOL over time in patients with HCC undergoing various treatment methods compared with baseline with (A) SF-12 or SF-36 and (B) EORTC. Ate, atezolizumab; Bev, bevacizumab; HR, hepatic resection; Len, lenvatinib; LT, liver transplantation

and combination TACE/RFA were largely associated with symptom improvements, whereas sorafenib was associated with shorter-term symptom improvement and longer-term worsening. The EORTC questionnaire showed short-term symptom worsening and subsequent symptom stability with TACE (Figure 4B). Data on transarterial radioembolization (TARE)/90-yttrium therapy are emerging and suggest that TARE is well tolerated in unresectable HCC, can help maintain HRQOL for longer compared to sorafenib, and is associated with smaller HRQOL decrements and symptoms than TACE, although studies are largely small, heterogeneous, and with variable comparison groups.[50,68–71] Data on radiotherapy are limited; a study by Iwata et al. showed that proton radiotherapy was associated with HRQOL preservation as measured by EORTC at 1 year among patients age 80 and older.[72]

DISCUSSION

HCC is associated with significant morbidity that impacts PROs stemming from several factors, including the presence of cancer itself, the severity of underlying cirrhosis, and adverse effects associated with HCC therapy. In this scoping review, we summarize the current state of knowledge about PROs in HCC with the aim of characterizing PROs that could better inform patient–clinician discussions, guide tailored treatment plans, and lead to quality improvement in clinical management of HCC.

Central themes

We found that several important themes dominate the literature on PROs in HCC care. First, the largest

contribution to PRO burden in patients with HCC is related to cirrhosis and other physical and psychiatric comorbidities rather than HCC itself. The most common symptoms independently related to HCC include bodily pain, fatigue, sexual dysfunction, and sleep disturbance, highlighting areas of need for symptom management in this population. Second, the severity of the underlying liver disease is a crucial determinant of poor PROs. Third, PROs are correlated with several patient-related factors, which can be interrelated with cirrhosis/HCC, including functional status and nutritional status.[73] Fourth, HRQOL is often independently associated with survival in patients with HCC, highlighting their potential role and value in treatment monitoring. Fifth, qualitative studies elicit concerns such as feelings of fear, stigma, specific symptoms related to systemic therapy, trade-offs between symptom burden and efficacy, as well as positive themes such as hope, acceptance, life meaning, and satisfaction. Finally, curative therapies are associated with improvement in PROs, whereas, as starkly depicted in Figures 3 and 4, palliative therapies are generally associated with deterioration of PROs, although the time course of PRO deterioration varies depending on treatment (locoregional vs. systemic). While many of the included studies examined HRQOL associated with sorafenib, several recent registration trials show that more efficacious therapies, particularly atezolizumab and bevacizumab, result in a superior HRQOL.

Persistent gaps

There are several gaps identified in our review that warrant attention in future studies. First, there is a paucity of high-quality data for certain populations of patients with HCC; data for locoregional therapies (TACE/TARE) and radiotherapy are still emerging. Many of the studies included are small and consisted of single-center cohorts that lacked power for meaningful subgroup analyses. Setting appropriate expectations of symptoms may help patients cope with side effects and better choose among treatment regimens with similar therapeutic efficacy; this is an area ripe for future study. HCC registration trials show efficacy and decreased adverse event burden with improvement in PROs; however, real-world data in patients receiving systemic therapy are still lacking. Second, the instruments to measure PROs can vary widely in their symptom assessment. Generic instruments such as the SF-36 and Short Form 8 have been broadly applied across health conditions and are well validated; however, may miss disease-specific symptoms/concerns important to patients with HCC and cirrhosis.[74] Disease-specific instruments, such as the FACT-Hep or QLQ-HCC-18, include HCC-specific measures but have fewer data to support their validity. For example, only a small proportion of patients in the FACT-Hep derivation and validation studies had HCC (7% and 19%, respectively), and critical parameters such as minimal important differences have not been established for the QLQ-HCC-18.[75,76] Qualitative studies highlighted a myriad of patient symptoms and concerns that may not be adequately captured by existing instruments. Further validation of disease-specific PRO instruments across health states, with more granular accounting for underlying liver disease, sex, and other sociodemographic factors, is necessary to ensure that the instruments capture the breadth of symptoms and concerns that patients with HCC experience.

Opportunities

Broadly, the opportunities in PRO research apply to further investigation and implementation. First, multicenter studies with common PRO measurement protocols could allow for better understanding or correlates (e.g., sociodemographics) of PROs as they relate to treatment of HCC. There may be important subgroup differences of patient experience stratified by underlying liver disease, sex, racial/ethnic, or socioeconomic factors. Given that the comparative efficacy on disease control of many of the therapies for HCC is emerging, systematic measurement of PROs can provide essential insights regarding the relative efficacy and tolerability of HCC therapy. Given the recent approval of multiple systemic therapies, there is a fundamental need to understand the impact of therapy on PROs when designing patient-centered, personalized treatment plans. As shown with other cancers, routine clinical measurement of PROs in HCC may lead to improved outcomes as PROs may elicit symptoms or concerns not otherwise captured in a clinical encounter.[77]

Second, the role of palliative care and other supportive care measures in PROs has not been systematically evaluated. Studies in other cancer types have shown that longitudinal HRQOL measurement in patients receiving palliative care can lead to referral for more aggressive symptom management.[78] Patients undergoing noncurative HCC therapy, including locoregional therapy, have deteriorating PROs representing major unmet needs that could be addressed with palliative care (Figures 3 and 4). It is also important to note the variability in symptom trajectories based on patient selection, study setting, duration of follow-up, and PRO instrument selected. Given the current evidence, specific PRO instruments cannot be recommended; however, evidence supports short-term worsening of HRQOL secondary to treatment, which may be transient, and expectedly more sustained worsening with tumor and liver disease progression.

Third, these data highlight the complex interplay between HCC stage and therapy with psychosocial and behavioral factors in determining a patient's HRQOL. As such, optimal management will require a multidisciplinary and holistic approach integrating hepatology, primary care, oncology, interventional radiology, and other specialties. It is unclear whether contemporary liver cancer clinics are equipped to provide such care. Approaches to addressing patient well-being will vary with the stage of disease as well as the patient's psychosocial comorbidities. For example, early-stage disease may benefit from management with primary care, social work or psychiatry, and hepatology, whereas intermediate-stage to late-stage disease may benefit from palliative care playing a central role.[79] Notably, caregivers of patients with HCC are an understudied group who likely have unmet needs in our current paradigms of care.

Finally, the implementation of PRO assessment in clinical care requires additional study. Assessments can be conducted in clinics using paper-based surveys, but this requires dedicated staff to administer, collect, and enter the data. Using the model that we developed with PRO-based metrics for cirrhosis, we selected a limited set of PROs that could be administered through the electronic medical record.[5] Electronic capture (e.g., patient completes assessment before appointment, while in waiting room, or at home in between treatments) is efficient and allows centers to regularly create reports for self-assessment and quality improvement. Design of PRO data capture, however, must account for patients with low health or digital literacy and limited English proficiency to avoid disparities in ascertainment. Studies will also need to assess how responses to those assessments may influence informed decision-making, treatment of symptoms, and advance care planning.

CONCLUSIONS

This scoping review has shown the breadth of the existing literature on PROs for HCC across the treatment continuum. We have highlighted several important findings and opportunities for future investigations. Further studies that integrate PROs into clinical practice and studies of comparative effectiveness of treatment impact on PROs across HCC stages will allow the development of robust quality of care indicators and enhance the quality of care for this group with high symptom burden and mortality. Although data are insufficient to recommend specific measures, evidence suggests that incorporating PRO measurement into clinical practice may reduce treatment-related anxiety, improve patient/caregiver well-being, and guide clinical management.[80]

CONFLICTS OF INTEREST

Dr. Serper consults for Gilead. Dr. Parikh advises Genentech, Bayer, and Eisai. Dr. Volk consults and is on the speakers' bureau for Bausch. Dr. Lake consults for HepQuant and Micromatrix. He received grants from Cymabay. Dr. Morgan received grants from Genfit, AbbVie, and Gilead.

AUTHOR CONTRIBUTIONS

Concept: Marina Serper, and Elliot B. Tapper. *Data acquisition:* Marina Serper, Elliot B. Tapper, Neehar D. Parikh, Grace Thiele, Nadia Ovchinisky, Shivang Mehta, Alexander Kuo, Chanda Ho, Fasiha Kanwal, Michael Volk, Sumeet K. Asrani, Marwan S. Ghabril, John R. Lake, Raphael B. Merriman, and Timothy R. Morgan. *Writing:* Marina Serper, Elliot B. Tapper, Neehar D. Parikh, and Grace Thiele. *Revision:* Nadia Ovchinisky, Shivang Mehta, Alexander Kuo, Chanda Ho, Fasiha Kanwal, Michael Volk, Sumeet K. Asrani, Marwan S. Ghabril, John R. Lake, Raphael B. Merriman, and Timothy R. Morgan.

ORCID

Marina Serper https://orcid.org/0000-0003-4899-2160
Neehar D. Parikh https://orcid.org/0000-0002-5874-9933
Nadia Ovchinsky https://orcid.org/0000-0002-1528-1680
Chanda Ho https://orcid.org/0000-0003-4068-6118
Fasiha Kanwal https://orcid.org/0000-0001-6715-3966
Sumeet K. Asrani https://orcid.org/0000-0001-9174-5670
Marwan S. Ghabril https://orcid.org/0000-0002-4784-3246
Timothy R. Morgan https://orcid.org/0000-0003-1328-0307
Elliot B. Tapper https://orcid.org/0000-0002-0839-1515

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Li L, Yeo W. Value of quality of life analysis in liver cancer: a clinician's perspective. World J Hepatol. 2017;9:867–83.
3. Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient Related Outcome Measures. 2018;9:353.
4. Kanwal F, Tapper EB, Ho C, Asrani SK, Ovchinsky N, Poterucha J, et al. Development of quality measures in cirrhosis by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. Hepatology. 2019;69:1787–97.
5. Tapper EB, Kanwal F, Asrani SK, Ho C, Ovchinsky N, Poterucha J, et al. Patient reported outcomes in cirrhosis: a scoping review of the literature. Hepatology. 2018;67:2375–83.

6. Feeny DH, Eckstrom E, Whitlock EP, Perdue LA. Patient-reported outcomes, health-related quality of life, and function: an overview of measurement properties. In A primer for systematic reviewers on the measurement of functional status and health-related quality of life in older adults. Rockville, MD: Agency for Healthcare Research and Quality. https://www.ncbi.nlm.nih.gov/books/NBK169156/
7. Pose E, Trebicka J, Mookerjee RP, Angeli P, Ginès P. Statins: old drugs as new therapy for liver diseases? J Hepatol. 2019;70:194–202.
8. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5:210.
9. Ryu E, Kim K, Cho MS, Kwon IG, Kim HS, Fu MR. Symptom clusters and quality of life in Korean patients with hepatocellular carcinoma. Cancer Nurs. 2010;33:3–10.
10. Bianchi G, Loguercio C, Sgarbi D, Abbiati R, Brunetti N, De Simone T, et al. Reduced quality of life of patients with hepatocellular carcinoma. Dig Liver Dis. 2003;35:46–54.
11. Chung M-H, Wang S-Y, Lin C-C. Symptom clusters and impact of fatigue and sleep disturbance on symptom experiences of hepatoma patients in Taiwan. Cancer Nurs. 2017;40:403–11.
12. Li L, Mo F, Hui EP, Chan SL, Koh J, Tang NLS, et al. The association of liver function and quality of life of patients with liver cancer. BMC Gastroenterol. 2019;19:66.
13. Qiao CX, Zhai XF, Ling CQ, Lang QB, Dong HJ, Liu Q, et al. Health-related quality of life evaluated by tumor node metastasis staging system in patients with hepatocellular carcinoma. World J Gastroenterol. 2012;18:2689–94.
14. Hsu W-C, Tsai AC, Chan S-C, Wang P-M, Chung N-N. Mini-nutritional assessment predicts functional status and quality of life of patients with hepatocellular carcinoma in Taiwan. Nutr Cancer. 2012;64:543–9.
15. Kondo Y, Yoshida H, Tateishi R, Shiina S, Mine N, Yamashiki N, et al. Health-related quality of life of chronic liver disease patients with and without hepatocellular carcinoma. J Gastroenterol Hepatol. 2007;22:197–203.
16. Mikoshiba N, Miyashita M, Sakai T, Tateishi R, Koike K. Depressive symptoms after treatment in hepatocellular carcinoma survivors: prevalence, determinants, and impact on health-related quality of life. Psycho-Oncology. 2013;22:2347–53.
17. Lee H-H, Chiu C-C, Lin J-J, Wang J-J, Lee K-T, Sun D-P, et al. Impact of preoperative anxiety and depression on quality of life before and after resection of hepatocellular carcinoma. J Affect Disord. 2019;246:361–7.
18. Hansen L, Dieckmann NF, Kolbeck KJ, Naugler WE, Chang MF. Symptom distress in patients with hepatocellular carcinoma toward the end of life. Oncol Nurs Forum. 2017;44:665–73.
19. 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. Psycho-Oncology. 2013;22:1353–60.
20. 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;16:203–15.
21. Steel J, Hess SA, Tunke L, Chopra K, Carr BI. Sexual functioning in patients with hepatocellular carcinoma. Cancer. 2005;104:2234–43.
22. Palmieri VO, Santovito D, Margari F, Lozupone M, Minerva F, Di Gennaro C, et al. Psychopathological profile and health-related quality of life (HRQOL) in patients with hepatocellular carcinoma (HCC) and cirrhosis. Clin Exp Med. 2015;15:65–72.
23. Moore AM, Gamblin TC, Geller DA, Youssef MN, Hoffman KE, Gemmell L, et al. A prospective study of posttraumatic growth as assessed by self-report and family caregiver in the context of advanced cancer. Psychooncology. 2011;20:479–87.
24. Bonnetain F, Paoletti X, Collette S, Doffoel M, Bouché O, Raoul JL, et al. Quality of life as a prognostic factor of overall survival in patients with advanced hepatocellular carcinoma: results from two French clinical trials. Qual Life Res. 2008;17:831–43.
25. Sternby Eilard M, Hagström H, Mortensen KE, Wilsgaard T, Vagnildhaug OM, Dajani O, et al. Quality of life as a prognostic factor for survival in hepatocellular carcinoma. Liver Int. 2018;38:885–94.
26. Cancer of the Liver Italian Program (CLIP) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology. 1998;28:751–5.
27. Gmür 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;38:1468–74.
28. Li L, Mo FKF, Chan SL, Hui EP, Tang NSL, Koh J, 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;17:8.
29. Kim G-A, Kim HI, Chang S, An J, Lee D, Lee HC, et al. A prospective evaluation of the reliability and utility of quality of life measures in patients with hepatocellular carcinoma. Am J Clin Oncol. 2019;42:555–63.
30. Deng Y, Zhu J, Liu Z, Huang M, Chang DW, Gu J. Elevated systemic inflammatory responses, factors associated with physical and mental quality of life, and prognosis of hepatocellular carcinoma. Aging (Albany NY). 2020;12:4357–70.
31. 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;24:1669–75.
32. Gill J, Baiceanu A, Clark PJ, Langford A, Latiff J, Yang P-M, et al. Insights into the hepatocellular carcinoma patient journey: results of the first global quality of life survey. Future Oncol. 2018;14:1701–10.
33. Fan SY, Eiser C. Illness experience in patients with hepatocellular carcinoma: an interpretative phenomenological analysis study. Eur J Gastroenterol Hepatol. 2012;24:203–8.
34. 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:E19–27.
35. 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;22:919–26.
36. Lo SH, Sharma R, Costentin CE, Aggio D, Shergill S, Colaone F, et al. Patient preferences for advanced hepatocellular carcinoma treatment: a multicountry stated preference study. Future Oncol. 2021;17:4275–87.
37. Lee E. Relationships among depressive symptoms, spiritual well-being, and quality of life in primary liver cancer patients in Korea. Dissertation. Case Western Reserve University; 2012.
38. Patel N, Maher J, Lie X, Gwaltney C, Barzi A, Karwal M, et al. Understanding the patient experience in hepatocellular carcinoma: a qualitative patient interview study. Qual Life Res. 2021. https://doi.org/10.1007/s11136-021-02903-4
39. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382:1894–905.
40. Galle PR, Finn RS, Qin S, Ikeda M, Zhu AX, Kim T-Y, 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;22:991–1001.
41. Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163–73.
42. Vogel A, Qin S, Kudo M, Su Y, Hudgens S, Yamashita T, 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;6:649–58.
43. Kudo M, Galle PR, Llovet JM, Finn RS, Vogel A, Motomura K, et al. Ramucirumab in elderly patients with hepatocellular carcinoma and elevated alpha-fetoprotein after sorafenib in REACH and REACH-2. Liver Int. 2020;40:2008–20.
44. Zhu AX, Nipp RD, Finn RS, Galle PR, Llovet JM, Blanc JF, 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:e000797.
45. Yau T, Kang Y-K, Kim T-Y, El-Khoueiry AB, Santoro A, Sangro B, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. JAMA Oncol. 2020;6:e204564.
46. Ryoo B-Y, Merle P, Kulkarni AS, Cheng A-L, Bouattour M, Lim HY, 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;127:865–74.
47. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux G-P, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017;18:1624–36.
48. Chow PKH, Gandhi M, Tan S-B, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. J Clin Oncol. 2018;36:1913–21.
49. Brunocilla PR, Brunello F, Carucci P, Gaia S, Rolle E, Cantamessa A, et al. Sorafenib in hepatocellular carcinoma: prospective study on adverse events, quality of life, and related feasibility under daily conditions. Med Oncol. 2013;30:345.
50. Salem R, Gilbertsen M, Butt Z, Memon K, Vouche M, Hickey R, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. Clin Gastroenterol Hepatol. 2013;11:1358–65.e1.
51. 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;136:693–9.
52. Huang G, Chen X, Lau WY, Shen F, Wang R-Y, Yuan S-X, et al. Quality of life after surgical resection compared with radiofrequency ablation for small hepatocellular carcinomas. Br J Surg. 2014;101:1006–15.
53. Wang Y-B, Chen M-H, Yan K, Yang W, Dai Y, Yin S-S. Quality of life after radiofrequency ablation combined with transcatheter arterial chemoembolization for hepatocellular carcinoma: comparison with transcatheter arterial chemoembolization alone. Qual Life Res. 2007;16:389–97.
54. 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:e23–30.
55. 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 Gastro Hepatol. 2012;24:186–94.
56. Chie W-C, Blazeby JM, Hsiao C-F, Chiu H-C, Poon RT, Mikoshiba N, et al. Differences in health-related quality of life between European and Asian patients with hepatocellular carcinoma. Asia Pac J Clin Oncol. 2017;13:e304–11.
57. Hinrichs JB, Hasdemir DB, Nordlohne M, Schweitzer N, Wacker F, Vogel A, et al. Health-related quality of life in patients with hepatocellular carcinoma treated with initial transarterial chemoembolization. Cardiovasc Intervent Radiol. 2017;40:1559–66.
58. Hartrumpf KJ, Marquardt S, Werncke T, Murray T, Kirstein MM, Vogel A, et al. Quality of life in patients undergoing repetitive TACE for the treatment of intermediate stage HCC. J Cancer Res Clin Oncol. 2018;144:1991–9.
59. Chau I, Peck-Radosavljevic M, Borg C, Malfertheiner P, Seitz JF, Park JO, 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.
60. Cao W, Li J, Hu C, Shen J, Liu X, Xu Y, et al. Symptom clusters and symptom interference of HCC patients undergoing TACE: a cross-sectional study in China. Support Care Cancer. 2013;21:475–83.
61. Lee L-H, Chen C-H, Yao G, Chung C-W, Sheu J-C, Lee P-H, et al. Quality of life in patients with hepatocellular carcinoma received surgical resection. J Surg Oncol. 2007;95:34–9.
62. Wible BC, Rilling WS, Drescher P, Hieb RA, Saeian K, Frangakis C, et al. Longitudinal quality of life assessment of patients with hepatocellular carcinoma after primary transarterial chemoembolization. J Vasc Interv Radiol. 2010;21:1024–30.
63. Chiu CC, Lee KT, Wang JJ, Sun DP, Lee HH, Huang CC, 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;8:576.
64. He Q, Jiang JJ, Jiang YX, Wang WT, Yang L. Health-related quality of life comparisons after radical therapy for early-stage hepatocellular carcinoma. Transplant Proc. 2018;50:1470–4.
65. Shomura M, Kagawa T, Okabe H, Shiraishi K, Hirose S, Arase Y, 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;16:878.
66. Shun SC, Chen CH, Sheu JC, Liang JD, Yang JC, Lai YH. Quality of life and its associated factors in patients with hepatocellular carcinoma receiving one course of transarterial chemoembolization treatment: a longitudinal study. Oncologist. 2012;17:732–9.
67. Hassanin TM, Fouad Y, Hassnine A, Eisawy M, Farag N, Abdel GW. 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;22:1255–61.
68. Loffroy R, Ronot M, Greget M, Bouvier A, Mastier C, Sengel C, 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;44:36–49.
69. Pereira H, Bouattour M, Burgio MD, Assenat E, Grégory J, Bronowicki J-P, 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.
70. Salem R, Hassan S, Lewandowski RJ, Grace K, Martin RCG, Sichlau MJ, et al. Quality of life after radioembolization for hepatocellular carcinoma using a digital patient-reported outcome tool. J Vasc Interv Radiol. 2020;31:311–4 e311.

71. Kirchner T, Marquardt S, Werncke T, Kirstein MM, Brunkhorst T, Wacker F, et al. Comparison of health-related quality of life after transarterial chemoembolization and transarterial radioembolization in patients with unresectable hepatocellular carcinoma. Abdom Radiol (NY). 2019;44:1554–61.
72. Iwata H, Ogino H, Hattori Y, Nakajima K, Nomura K, Hayashi K, et al. Image-guided proton therapy for elderly patients with hepatocellular carcinoma: high local control and quality of life preservation. Cancers (Basel). 2021;13:219.
73. Gunsar F, Raimondo ML, Jones S, Terreni N, Wong C, Patch D, et al. Nutritional status and prognosis in cirrhotic patients. Aliment Pharmacol Ther. 2006;24:563–72.
74. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care. 1989;27:S217–32.
75. Heffernan N, Cella D, Webster K, Odom L, Martone M, Passik S, 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;20:2229–39.
76. Blazeby JM, Currie E, Zee BC, Chie WC, Poon RT, Garden OJ. 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;40:2439–44.
77. Basch E, Deal AM, Dueck AC, Scher HI, Kris MG, Hudis C, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA. 2017;318:197–8.
78. Stukenborg GJ, Blackhall LJ, Harrison JH, Dillon PM, Read PW. Longitudinal patterns of cancer patient reported outcomes in end of life care predict survival. Support Care Cancer. 2016;24:2217–24.
79. Verma M, Tapper EB, Singal AG, Navarro V. Nonhospice palliative care within the treatment of end-stage liver disease. Hepatology. 2020;71:2149–59.
80. Denis F, Basch E, Septans AL, Bennouna J, Urban T, Dueck AC, et al. Two-year survival comparing web-based symptom monitoring vs routine surveillance following treatment for lung cancer. JAMA. 2019;321:306–7.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Serper M, Parikh ND, Thiele G, Ovchinsky N, Mehta S, Kuo A, 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;76:251–274. https://doi.org/10.1002/hep.32313