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Patient-Reported Outcomes in HCC: A Scoping Review by the Practice Metrics Committee of the American Association for the Study of Liver Diseases

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List of Abbreviations:

AJCC American Joint Committee on Cancer
BCLC Barcelona Clinic Liver Cancer
EORTC European Organization for Research and Treatment of Cancer
HCS Hepatobiliary Cancer Subscale
FACT-Hep Functional Assessment of Cancer Therapy, Hepatobiliary
HRQOL health-related quality of life
LT liver transplantation
PRO patient-reported outcome
QLQ-C30 Quality of Life Questionnaire Core-30
QOL quality of life
SF-36 Short Form 36
TACE transarterial chemoembolization
TARE transarterial radioembolization

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Abstract

Background & Aims: Hepatocellular carcinoma (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 & 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, 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 will 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 the **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-5D, etc.), more general PRO terminology (e.g., patient satisfaction, health-related quality of life [HRQOL], quality of life [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 nonstandard 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 Practice Metrics Committee for relevance. Full-text documents were then retrieved and also 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 was 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 manuscripts 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 symptoms 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 4 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 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 found to be 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 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 with 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 7 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. 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 HCC18 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 HCC18 nutrition scale to the Cancer of the Liver Italian Program score.(26) In a prospective single-center study of 242 patients, Gmür et al. showed that the FACT-Hep questionnaire improves prognostication beyond ECOG performance status.(27) Li et al.

investigated the prognostic significance of Quality of Life Questionnaire-C30 (QLQ-C30), QLQ-HCC18, and C30/HCC18 index scores in patients with newly diagnosed HCC of various stages.(28) A higher symptom burden on theQLQ-C30 index and QLQ-HCC18 was associated with higher adjusted mortality. Kim et al. evaluated EORTC QLQ-30, QLQ-HCC18, and FACT-Hep in a Korean cohort of 300 patients and found that EORTC role functioning and the hepatobiliary cancer subscale (HCS) of the FACT-Hep enhanced the prediction of 1-year survival when added to conventional cancer staging systems (AJCC and BCLC). 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 poor physical and/or mental HRQOL on the 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-naïve HCC using QLQ-C30 and QLQ-HCC18 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 semi-structured 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 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 conducted 10 semi-structured interviews with 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 Europeans 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 were associated with a reduced risk of deterioration on all QLQ-C30 generic cancer symptom scales (appetite loss, diarrhea, fatigue, pain) and several QLQ-HCC18 disease-specific symptom scales (fatigue, pain) when compared to sorafenib. Atezolizumab-bevacizumab vs. 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 III REFLECT trial (lenvatinib vs. sorafenib), baseline HRQOL scores were similar and declined in both groups following initiation of treatment. Time to clinically meaningful deterioration in role functioning, pain, and diarrhea (QLQ-C30), nutrition, and body image (QLQ-HCC18), and EQ-5D 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 III 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 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 II 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 III KEYNOTE-240 study (pembrolizumab vs. placebo), from baseline to week 12 changes in both EORTC QLQ-C30 and QLQ-HCC18 scores and time to deterioration were similar for both arms.(46)

Two Phase III trials have evaluated radioembolization versus sorafenib for the treatment of unresectable HCC. In the SARAH trial, the global health status subscore was significantly better with radioembolization (Y90) group than 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 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 **Figs. 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 **Supporting Fig. 3**). In the Functional Assessment of Chronic Illness Therapy questionnaire (**Fig. 3**), locoregional therapy (largely TACE) was generally associated with symptom deteriorations as were sorafenib and best supportive care. When assessed with Short Form 12, SF-36, and EORTC QLQ instruments (**Fig. 4A**), curative therapies, TACE, 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 (**Fig. 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 predominate the literature in 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, tradeoffs 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 **Figs. 3** and **4**, palliative therapies are generally associated with deterioration of PROs, although the time course of PRO deterioration varies depending on treatment (locoregional versus 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 lacking 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 AE burden track 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 SF-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-HCC18, 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-HCC18.(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 in ensuring 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) As shown in **Figures 3** and **4**, patients undergoing noncurative HCC therapy, including locoregional therapy, have deteriorating PROs representing major unmet needs that could be addressed with palliative care. 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-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 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)

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Figure legends

Figure 1. Most commonly used validated PRO questionnaires in HCC. Abbreviations: QLQ-HCC18, HCC-specific domain of QLQ; FACIT, Functional Assessment of Cancer Therapy; FHSI-8, FACT Hepatobiliary Symptom Index-8; SF-12, Short Form 12.

Figure 2. Dominant themes elicited in qualitative studies.

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. Abbreviation: Y90, 90-yttrium therapy.

Figure 4. Changes in HRQOL over time in patients with HCC undergoing various treatment methods compared with baseline with (A) Short Forms (Short Form 12, SF-36) and (B) EORTC. Abbreviations: HR, hepatic resection; LT, liver transplantation; RFA, radio frequency ablation.

Table 1. Baseline Factors associated with Health-Related Quality of Life in Hepatocellular Carcinoma

Reference	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. (2002)	SF-36, NHP	(+) HCC	101	A (35%) B (43%) C (22%)	Not reported	Not reported	(+) cirrhosis (+) HBV and/or HCV (75%) (+) co-morbidity (64%)	QoL in patients with cirrhosis + HCC	(+): age, male gender (-): sleep disorders, daily medications, associated diseases, HCC diameter
		(+) cirrhosis, (-) HCC	202	A (39%) B (41%) C (20%)	N/A	N/A	(+) cirrhosis (+) HBV and/or HCV (69%) (+) co-morbidity (66%)		
Kondo et al. (2007)	SF-36	(+) HCC	97	A (77%) B (21%) C (2%)	Not reported	(+) PEIT or RFA	(+) recurrence (63%) (+) HBV (14%) (+) HCV (84%)	Comparison of HRQoL between HCC + non-HCC CLD patients	(+): serum albumin, prothrombin activity (-): age (PCS), female sex (PCS), presence of ascites (PCS), platelet count (PCS)
		(+) CLD, (-) HCC	97	A (89%) B (11%)	N/A	N/A	(+) HBV (10%) (+) HCV (88%)		
Hsu et al. (2012)	EORTC QLQ- C30	N/A	300	A (67%) B (29%) C (3%)	AJCC I (7%), II (34%), III (42%), IV (16%)	Not reported	(+) HBV (54%) (+) HCV (51%)	QoL evaluation using nutrition-based instrument	(+): nutritional status, hemoglobin, albumin, self-rated health status, motility (-): tumor staging, CTP score, WBC count, CRP, AFP level, GGT
Li et al. (2019)	EORTC QLQ- C30 and HCC18	N/A	517	A (67%) B (28%) C (5%)	Not reported	None	(+) cirrhosis (59%) (+) HBV (82%) (+) HCV (6%)	Correlation between baseline QoL + liver function	(+): albumin, albumin-to-ALP ratio (-): ALBI grade, ascites, MELD, CTP score, bilirubin, INR, ALP, ALT
Steel et al. (2006)	FACT-Hep	(+) HCC	83	A (51%) B (26%) C (1%)	TNM I&II (20%), III&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. (2010)	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. (2012)	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. (2017)	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: Measures: *SF,* Short Form; *NHP,* Nottingham Health Profile; *EORTC*, European Organisation for Research and Treatment of Cancer; *FACT*, Functional Assessment of Cancer Therapy; *MDASI-T,* M.D. Anderson Symptom Inventory; Demographics & disease state: *CTP*, Child-Turcotte-Pugh (score or class); *AJCC*, American Joint Committee on Cancer staging; *TNM*, TNM classification of malignant tumors; *HBV,* hepatitis B virus; *HCV*, hepatitis C virus Aims & prognostic factors: *PCS,* physical component score (SF); *WBC,* white blood cells; *CRP,* ; *AFP*, alpha-fetoprotein; *GGT,* gamma-glutamyl transpeptidase; *ALBI,* albumin-bilirubin grade; *MELD,* model for end-stage liver disease; *INR,* international normalized ratio; *ALP,* alkaline phosphatase; *ALT,* alanine aminotransferase; *HBS*, hepatobiliary subscale

Table 2. Psychosocial and psychological factors associated with Health-Related Quality of Life in Hepatocellular Carcinoma

Reference	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. (2013)	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, anxiety, obsessive-compulsive and hostility items
Fan et al. (2013)	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 illness perception, emotion-oriented coping, cognitive representation, emotional representation
Mikoshiba et al. (2013)	EORTC QLQ-C30 and HCC18	N/A	128	A (76%) B&C (24%)	Not reported	Curative treatment	(+) HBV (34%) (+) HCV (59%) (+) co-morbidity (65%)	Association of depressive symptoms + QoL, characterization in HCC survivors	QoL: (-): depressive symptoms Depressive symptoms: (+) KPS; (-): CTP score, living alone, unemployment
Steel et al. (2005)	FACT-Hep, Sexual History Questionnaire	(+) HCC	21	A (73%) B (18%)	TNM III (5%), IV (95%)	Not reported	Entirely men (+) cirrhosis (84%) (+) HBV (13%)	Evaluation of sexual morbidities in HCC population	(-): sexual problems

							(+) HCV (44%)		
		(+) CLD	23	A (67%) B (27%) C (6%)	N/A		Entirely men (+) cirrhosis (88%) (+) HCV (57%)		
Moore et al. (2010)	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
Lee et al. (2019)	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 HCC patients following resection	(-): anxiety, depression
Hansen et al. (2017)	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:

Therapy: *HR,* hepatic resection; *TACE*, transarterial chemoebolization; *TAE,* transarterial embolization

Measures: *SF,* Short Form, *SCL-90-R*, Symptom Checklist 90-R; *TAS-20,* Toronto Alexithymia Scale; *Hamilton-D,* Hamilton Depression rating scale; *EORTC*, European Organisation for Research and Treatment of Cancer; *FACT*, Functional Assessment of Cancer Therapy; *BAI,* Beck Anxiety Inventory; *BDI,* Beck Depression Inventory; *MSAS*, Memorial Symptom Assessment Scale; *CES-D*, *Center for Epidemiological Studies Depression Scale; PTG*, post-traumatic growth

Demographics & disease state: *CTP*, Child-Turcotte-Pugh (score or class); *BCLC*, Barcelona Clinic Liver Cancer staging; *AJCC*, American Joint Committee on Cancer staging; *TNM*, TNM classification of malignant tumors; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus

Aims & prognostic factors: *AFP*, alpha-fetoprotein; *KPS,* Karnofsky performance score

Table 3. Health-Related Quality of Life as a Prognostic Factor in Hepatocellular Carcinoma

Reference	PRO Measure(s)	Sample size	CTP Class	Staging	Prior therapy?	Other notes	Aims	Proposed prognostic factors for survival
Meier et al. (2015)	EORTC QLQ- C30 and HCC18	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

Eilard et al. (2017)	EORTC QLQ- C30 and HCC18	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 naïve	(+) cirrhosis (74%) (+) HCV (50%) (+) HBV (8%) (+) co-morbidity (58%)	Improvement of prognostication of survival with QoL	(+): physical functioning; (-): fatigue, nutrition, BCLC stage, CLIP stage, CTP score, TNM stage, AFP level, ECOG PS
Li et al. (2017)	EORTC QLQ- C30 and HCC18	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, HCC18 index score, C30 index score, albumin (-): pain, fatigue, metastases, multifocal or diffuse HCC, PVT, total bilirubin, AFP, ALP, creatinine
Kim et al. (2019)	EORTC QLQ- C30 and HCC18	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
Gmur et al. (2017)	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. (2020)	SF-12	735	A (79.5%)	TNM III & 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
Bonnetain et al. (2008)	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 QoL	(+) Spitzer score, albumin, small HCC; (-): jaundice, hepatomegaly, hepatalgia, ascites, PVT, AFP level, total bilirubin

Abbreviations:

Therapy: *TACE*, transarterial chemoebolization; *HR,* hepatic resection; *LT,* liver transplantation; *SIRT*, selective internal radiation therapy

Measures: *EORTC*, European Organisation for Research and Treatment of Cancer; *FACT*, Functional Assessment of Cancer Therapy; *PCS*, physical component score; *MCS*, mental component score

Demographics & disease state: *CTP*, Child-Turcotte-Pugh (score); *BCLC*, Barcelona Clinic Liver Cancer staging; *TNM*, TNM classification of malignant tumors; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus

Aims & prognostic factors: *CLIP,* Cancer of the Liver Italian Program staging; *AFP*, alpha-fetoprotein; *ECOG PS*, Eastern Cooperative Oncology Group performance status; *ALP*, alkaline phosphatase; *PIVKA-II*, protein-induced by vitamin K absence or antagonist-II; *SIR*, systemic inflammatory response; *WBC*, white blood cells; *NLR*, neutrophils-to-lymphocyte ratio; *LMR*, lymphocytes-to-monocytes ratio; *PVT*, portal vein thrombosis; *HBS*, hepatobiliary subscale

Table 4. Effects of Hepatocellular Carcinoma Therapy on Health-Related Quality of Life

Reference	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. (2017)	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. (2018)	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. (2020)	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. (2021)	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. (2021)	EORTC QLQ-C30 + HCC-18	Atezolizumab + bevacizumab	336	Not reported	Not reported	Treatment naïve		HRQoL comparison between atezolizumab + bevaciumab and sorafenib	N/A
		Sorafenib	165	Not reported	Not reported				N/A
Ryoo et al. (2021)	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. (2017)	FHSI-8 EQ-5D EQ-5D-VAS	Ramucirumab (ITT)	283	A (98%) B&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&C (2%)	BCLC B (12%), C (88%)		(+) HCV (35.3%) (+) HBV (35.8%)		N/A
Zhu et al. (2020)	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. (2020)	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. (2018)	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
Yau et al. (2020)	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%)	Evaluatiion of safety and efficacy of NV + IP in advanced HCC	N/A
		NV (3 mg/kg) + IP (1	49	A (96%)	BCLC 0 (0%), A (0%), B		(+) HBV (43%)		N/A

		mg/kg) every 3 weeks, then NV (240 mg) every 2 weeks			(8%), C (92%)		(+) HCV (29%)		
		NV (3 mg/kg) every 2 weeks + IP (1 mg/kg) every 6 weeks	49	A (96%)	BCLC 0 (0%), A (0%), B (6%), C (94%)		(+) HBV (53%) (+) HCV (24%)		N/A
Real-World Evidence									
Shomura et al. (2016)	SF-36	Sorafenib	54	A (76%) B (24%)	TNM III (43%), IV (57%)	Yes (91%)	(+) HCV (44%) (+) HBV (20%)	Longitudinal HRQoL after sorafenib, prognostic factors	(+): previous curative therapy, physical and social functioning; (-): vascular invasion, CTP, DCP
Chiu et al. (2019)	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; (-): co-morbidities
Wible et al. (2010)	SF-36	TACE	73	A (47%) B (51%) C (3%)	Okuda 1 (55%), 2 (42%), 3 (3%)	None		Longitudinal HRQoL after 1st TACE	N/A
He et al. (2018)	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
Shun et al. (2012)	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 1st TACE, prognostic factors	PCS: (+): age, recurrent disease; MCS: (-): male, recurrent disease
Iwata et al. (2021)	EORTC QLQ-C30 and HCC18 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%); Okuda I (87%), II (13%)	Yes (35%)	(+) HBV (10%) (+) HCV (39%)	Safety and efficacy of IGPT in elderly cohort	(+) female sex, primary tumor (-) ECOG PS, CTP score, high AFP levels, high PIVKA-II leveels
Lee et al. (2007)	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. (2017)	EORTC QLQ-C30 + HCC18	Resection	53	A (92%) B&C (8%)	BCLC A (91%), B&C (9%)	Yes (28%)	(+) cirrhosis (64%) (+) co-morbidity (51%)	Longitudinal HRQoL comparison between resection + RFA + TACE; domain MIDs	N/A
		RFA	53	A (70%) B&C (30%)	BCLC A (58%), B&C (42%)	Yes (70%)	(+) cirrhosis (81%) (+) co-morbidity (79%)		N/A
		TACE	65	A (75%) B&C (25%)	BCLC A (37%), B&C (63%)	Yes (69%)	(+) cirrhosis (68%) (+) co-morbidity (60%)		N/A
Hinrichs et al. (2017)	EORTC QLQ-C30 + HCC18	TACE	79	A (76%) B (19%)	Not reported	None		HRQoL after 1st TACE, prognostic factors	(+) symptom score; (-) MELD, CTP, ECOG PS, GHS and functional scores
Hartrumpf et al. (2018)	EORTC QLQ-C30 + HCC18	TACE	148	A (74%) B&C (26%)	Not reported	None	(+) HCV (30%) (+) HBV (18%)	HRQoL after repetitive TACE, prognostic factors	(+) symptom score; (-) GHS and functional scores
Kirchner et al. (2019)	EORTC QLQ-C30 + HCC-18	TACE	47	A (78.3%) B (21.7%)	Not reported	Treatment naïve	(+) cirrhosis (56.5%) (+) HBV (4.3%) (+) HCV (17.4%)	HQoL comparison between TACE and TARE for unresectable HCC	(+) less fever (-) female sex
		TARE	27	A (85.7%) B (14.3%)	Not reported	Treatment naïve	(+) cirrhosis (47.6%) (+) HBV (9.5%) (+) HCV (14.3%)		(-) female sex, higher age
Hassanin et al. (2021)	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. (2021)	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+6 (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. (2021)	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. (2013)	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. (2013)	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. (2001)	FACT-G	Resection	66	A (94%) B&C (6%)	TNM I (3%), II (44%), III (47%), IV (6%)	Yes (69%)	(+) cirrhosis (41%) (+) co-morbidity (27%)	Longitudinal HRQoL evaluation after resection	(-) TNM staging, recurrent disease
		TACE	10	Not reported	Not reported	Not reported	Inoperable HCC		N/A
Huang et al. (2014)	FACT-Hep	RFA	121	Not reported	BCLC A	None	(+) HBV (+) cirrhosis (79%) (+) co-morbidity (23%)	Longitudinal HRQoL + survival comparison between resection + RFA	(+) anti-viral treatment; (-) cirrhosis, co-morbidities
		Resection	225				(+) HBV (+) cirrhosis (88%) (+) co-morbidity (18%)		
Wang et al. (2007)	FACT-G	TACE	40	A (80%) B (20%)	TNM I&II (48%), III (13%), IV (40%)	None	(+) co-morbidity (73%)	HRQoL comparison between TACE alone + TACE-RFA	(+) income; (-) recurrent disease, post-treatment CTP
		TACE+RFA	43	A (79%) B (21%)	TNM I&II (49%), III (7%), IV (44%)	None	(+) co-morbidity (56%)		(+) age; (-) recurrent disease, post-treatment CTP
Toro et al. (2012)	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. (2012)	FACT-Hep	Resection+thrombectomy	65	A&B (76%) C (24%)	BCLC C	Not reported		Comparison of outcomes, survival, and HRQoL between HR + thrombectomy and chemotherapy	N/A
		Chemotherapy	50	A&B (75.4%) C (24.6%)					

Salem et al. (2020)	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
Cao et al. (2013)	MDAS-I	TACE	155	A (94%) B (6%)	BCLC A (27%), B (41%), C (32%)	None		Cross-sectional symptom PCA after 1st TACE	N/A

Abbreviations:

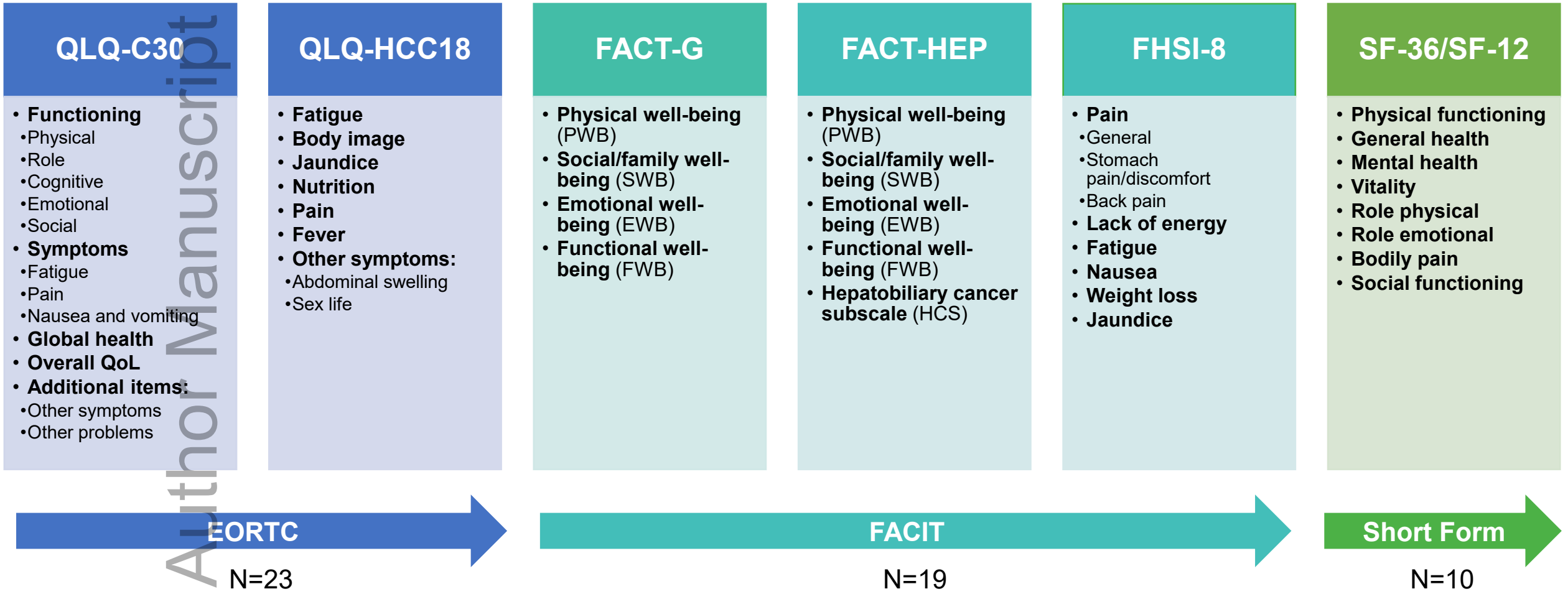
Therapy: *TACE*, transarterial chemoebolization; *RFA*, radiofrequency ablation; *TARE*, transarterial radioembolization; *IGPT*, image-guided proton therapy; *NV*, nivolumab; *IP*, ipillumumab; *Y-90*, 90-yttrium therapy; *ITT*, intention to treat; *PBO*, placebo

Measures: *SF*, short form; *SDS*, Symptom Distress Scale; *HADS*, Hospital Anxiety and Depression Scale; *EORTC*, European Organisation for Research and Treatment of Cancer; *FACT*, Functional Assessment of Cancer Therapy; *FHSI-8*, Functional Hepatobiliary Symptom Index – 8 items; *EQ-5D*, EuroHRQoL – 5 Dimensions; *VAS*, Visual Analogue Scale; *MDASI*, M.D. Anderson Symptom Inventory, *VAS*, Visual Analogue Scale, *WHO*, World Health Organization

Demographics & disease state: *CTP*, Child-Turcotte-Pugh (score); *TNM*, TNM classification of malignant tumors; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *BCLC*, Barcelona Clinic Liver Cancer staging; *UNOS*, United Network for Organ Sharing T staging; *PVTT*, portal vein tumor thrombi

Aims & prognostic factors: *MID*, minimally important difference; *MCID*, minimal clinically important difference; *DCP*, des-gamma carboxyprothrombin; *BMI*, body mass index; *PCS*, Physical Component Summary (score); *MCS*, Mental Component Summary (score); *AFP*, alpha-fetoprotein; *mRECIST*, modified response evaluation criteria in solid tumors; *MELD*, model for end-stage liver disease; *ECOG PS*, Eastern Cooperative Oncology Group performance status; *GHS*, global health status; *RCT*, randomized clinical trial; PCA, principal component analysis

Figure 1. Most commonly-used validated patient-reported outcome questionnaires in hepatocellular carcinoma



Abbreviations: PRO – patient-reported outcomes, HCC-hepatocellular carcinoma, EORTC-QLQ-C30 – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, FACIT-Functional Assessment of Cancer Therapy, FACT-Hep – Functional Assessment of Cancer Therapy, Hepatobiliary, FHSI-8 - FACT Hepatobiliary Symptom Index-8, SF-12 - Short Form 12-item, SF-36 – Short Form Health Survey-36

Figure 2. Dominant Themes Elicited in Qualitative Studies

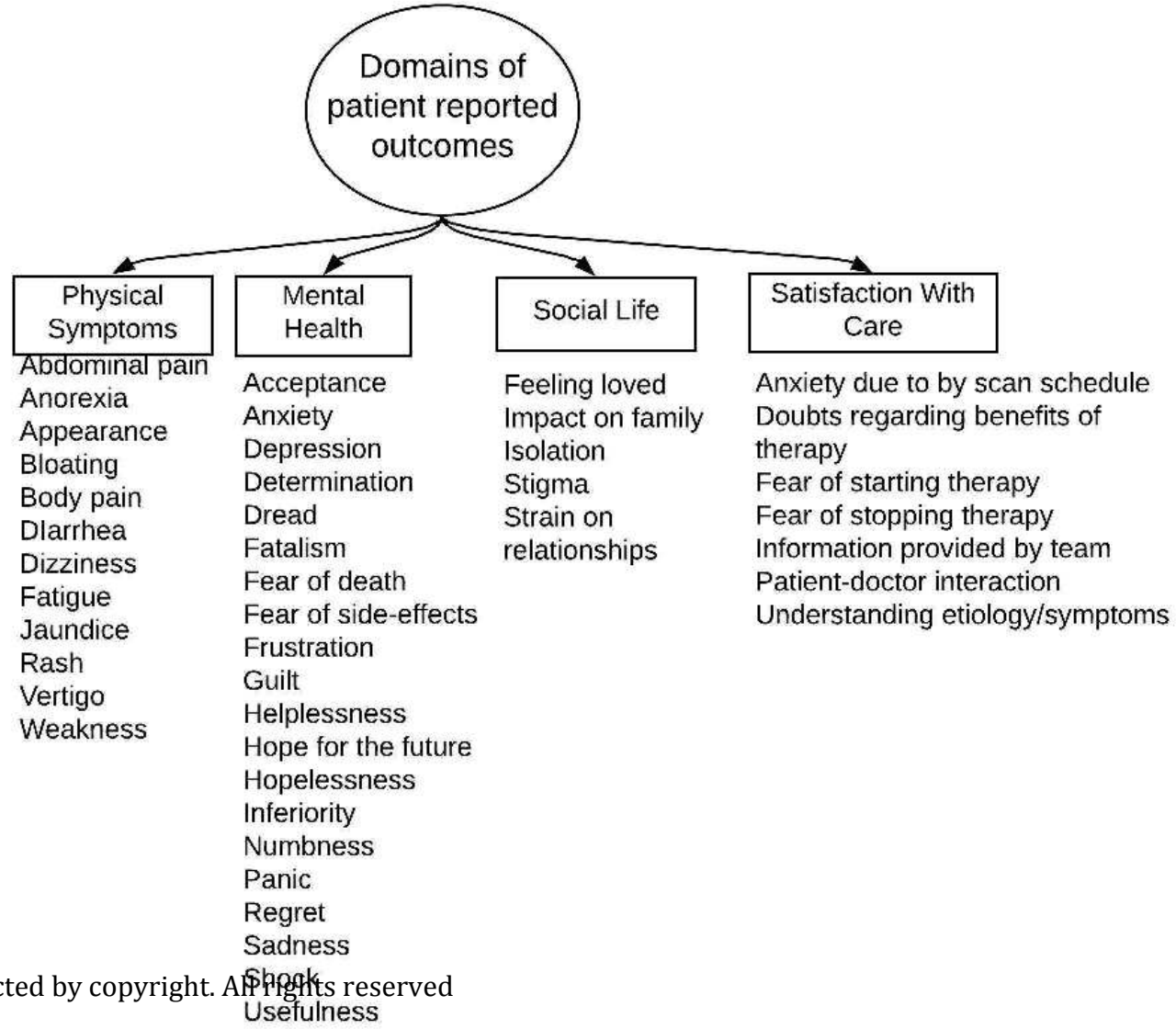
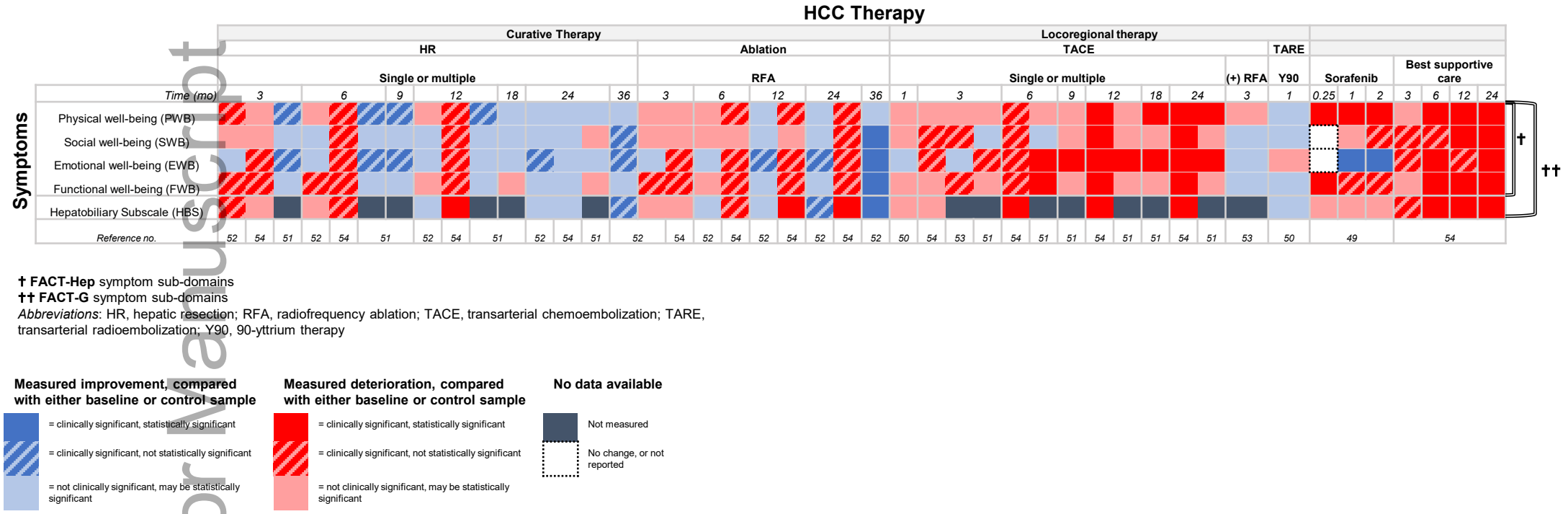
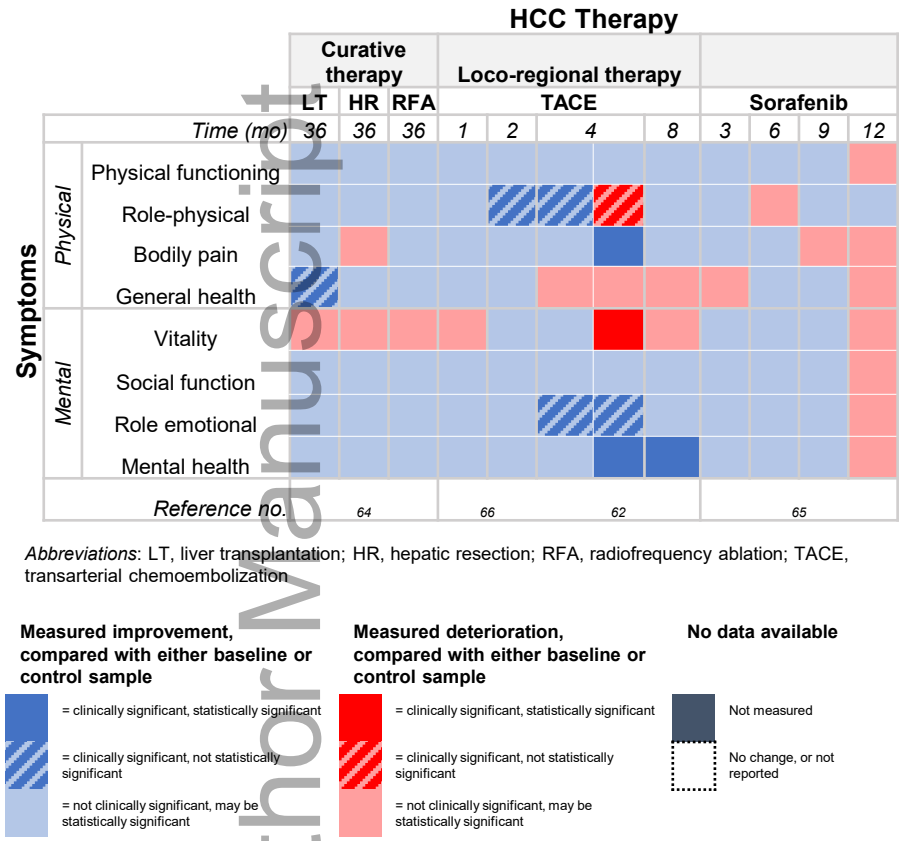


Figure 3. Changes in quality of life over time of HCC patients undergoing various treatment methods compared to baseline, as reported by Functional Assessment of Chronic Illness Therapy (FACIT) Patient Reported Outcome Measures.



† **FACT-Hep** symptom sub-domains
†† **FACT-G** symptom sub-domains
Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; Y90, 90-yttrium therapy

A) Changes in quality of life over time of HCC patients undergoing various treatment methods, as reported by Short Form Patient Reported Outcome Measures.



Abbreviations: LT, liver transplantation; HR, hepatic resection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization

Measured improvement, compared with either baseline or control sample

= clinically significant, statistically significant

= clinically significant, not statistically significant

= not clinically significant, may be statistically significant

Measured deterioration, compared with either baseline or control sample

= clinically significant, statistically significant

= clinically significant, not statistically significant

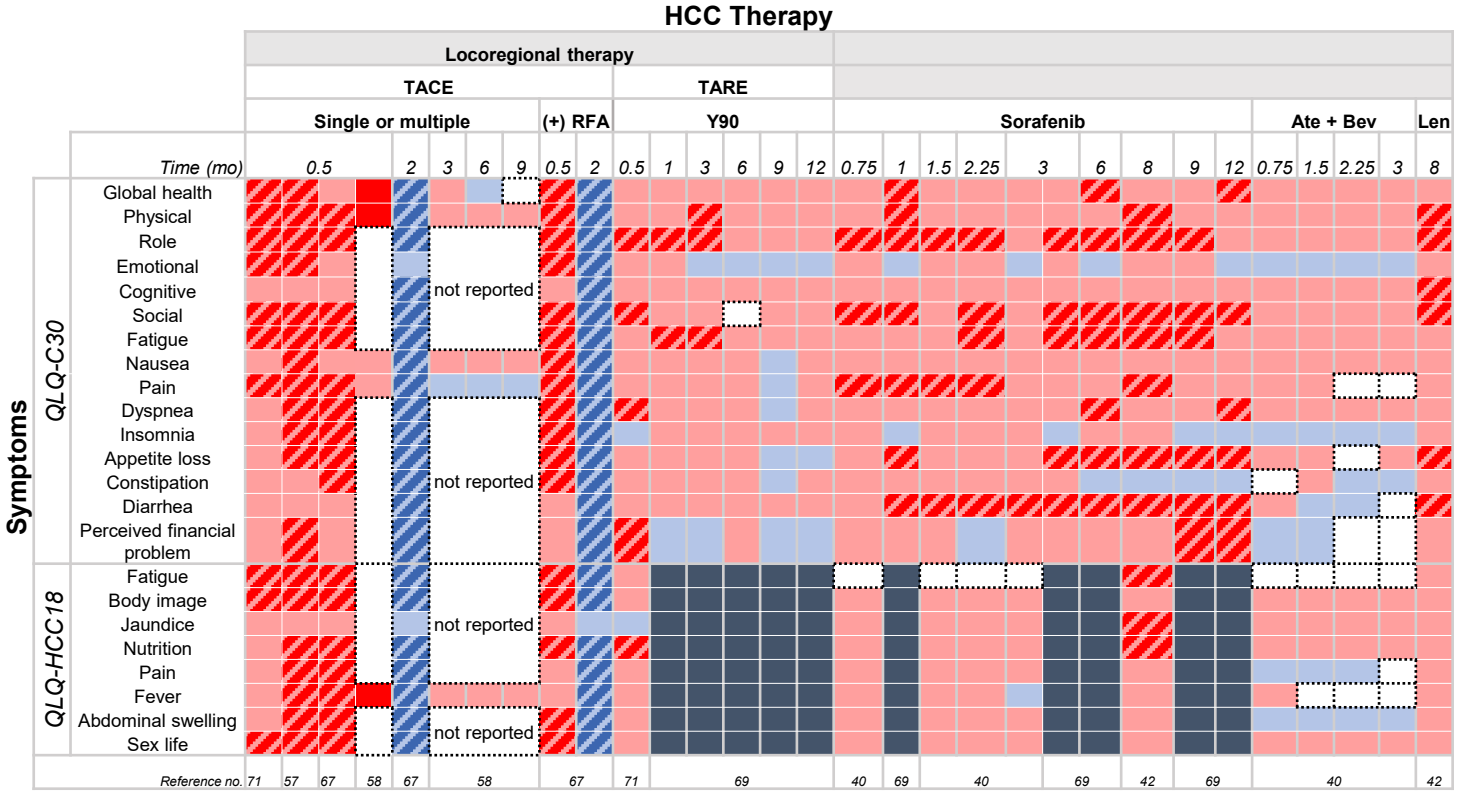
= not clinically significant, may be statistically significant

No data available

Not measured

No change, or not reported

B) Changes in quality of life over time of HCC patients undergoing various treatment methods, as reported by European Organization for Research and Treatment of Cancer (EORTC) Patient Reported Outcome Measures.



Abbreviations: TACE, transarterial chemoembolization; TARE, transarterial radioembolization; Y90, 90-yttrium therapy; Ate, atezolizumab; Bev, bevacizumab; Len, lenvatinib

Measured improvements, compared with either baseline or control sample

= clinically significant, statistically significant

= clinically significant, not statistically significant

= not clinically significant, may be statistically significant

Measured deterioration, compared with either baseline or control sample

= clinically significant, statistically significant

= clinically significant, not statistically significant

= not clinically significant, may be statistically significant

No data available

Not measured

No change, or not reported

Figure 4.