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Systematic Review of Studies Assessing the Health-Related Quality of Life of Hepatocellular Carcinoma Patients from 2009 to 2018

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We reviewed all studies assessing the health-related quality of life (HRQoL) in patients with hepatocellular carcinoma (HCC) between 2009 and 2018 (n = 45). Most studies assessed HRQoL as an outcome, and evaluated or compared the HRQoL of HCC patients depending on the type of treatment or stage of disease. HCC patients had a worse HRQoL than the general population, including in those with early-stage HCC. Patients commonly experienced pain, fatigue, sleep disturbance, distress, and lack of appetite, and these symptoms remained problematic even a few years after treatment. TNM classification of malignant tumors stage, tumor stage, presence of cirrhosis, being Asian, being female, living alone, or being unemployed were associated with a poor HRQoL. While recent studies have included a more diverse patient population, various topics, and different study designs, there were limited studies on supportive interventions. Given the increase in HCC cases and HCC survivors, addressing the HRQoL of HCC patients requires more attention.

Keywords: *Hepatocellular carcinoma; Quality of life; Systematic review*

INTRODUCTION

Health-related quality of life (HRQoL) is defined as how well a person functions in their life and their perceived well-being in the physical, mental, and social domains of health (1). Recently, HRQoL has been considered a strong predictor of survival in cancer patients (2, 3). In addition, understanding the impact of treatment on HRQoL could help physicians guide patients when deciding between two equally efficacious treatments (4, 5). Furthermore, HRQoL is becoming a major factor for evaluating therapeutic interventions in patients with diseases that are difficult to cure to help patients remain symptom-free, or at least to reduce the disease burden (4, 5).

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer (6, 7). HCC patients have a high mortality rate, with the relative survival rates being 31.0% in 2013–2016 (8). HCC treatment is mainly palliative, unless the disease is in its early stage. HCC patients suffer from symptoms such as sleep disorders, sexual dysfunction, ascites, gynecomastia, pruritus, fatigue, and muscle cramps, in addition to a negatively affected HRQoL (9). According to the Korean Liver Cancer Association–National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma, the ultimate goal of treatment in HCC patients is to increase the survival time and rate, and to the improve HRQoL. This requires multidisciplinary treatment planning in various fields, including gastroenterology, hepatology, oncology, surgery, radiology, interventional

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radiology, radiation oncology, pathology, and many other departments (10). HRQoL can be affected by treatment of HCC.

During the past 10 years, there have been dramatic changes in the prevention, diagnosis, and treatment of HCC (11). Active surveillance was promoted among populations at risk of developing HCC, such as people with hepatitis B virus or hepatitis C virus infection, thus enabling early diagnosis (12). The emergence of multiple new treatment modalities has changed the HCC treatment paradigm (13). Local tumor-directed therapies have significantly improved, such as radio-frequency ablation (RFA) and novel agents for transarterial chemoembolization (TACE). Furthermore, there have been improvements in procedures such as hepatic resection and liver transplantation. In addition, sorafenib was approved in 2017 as the first effective systemic treatment for HCC. Positive sorafenib results in advanced HCC patients prompted the evaluation of several first- and second-line agents for the treatment of HCC (14). As numerous trial and observational studies have evaluated the effects of these new treatments (11), an increasing number of studies have assessed the HRQoL of HCC patients. In terms of systematic reviews focusing on the HRQoL of HCC patients, there were two review papers published between 1985 and 2013 (15, 16). However, these papers did not include recent studies, which reflect new HCC management strategies. A recent narrative review included studies from 2001 to 2017, but it aimed to review measurement tools to assess HRQoL in HCC patients, and not the study design and outcomes related to HRQoL (17). Thus, this systematic review aims to evaluate studies assessing the HRQoL of HCC patients from 2009 to 2018.

MATERIALS AND METHODS

Information Sources and Search

Two authors performed the 1st and 2nd literature screening. Studies were identified by searching electronic databases, scanning reference lists of articles, and consulting with experts in the field. Database searches were conducted using Cochrane Library, PsychINFO, Embase, and PubMed. First, we searched PubMed for all English-language studies that assessed the HRQoL of HCC patients, published between 2009 and 2018, using the following terms: 1) hepatocellular carcinoma: "Carcinomas, Hepatocellular" OR "Hepatocellular Carcinomas" OR "Liver Cell Carcinoma, Adult" OR "Liver Cancer, Adult" OR "Adult Liver Cancer" OR "Adult Liver Cancers" OR "Cancer, Adult Liver" OR "Cancers, Adult Liver" OR "Liver Cancers, Adult" OR "Liver Cell Carcinoma" OR "Carcinoma, Liver Cell" OR "Carcinomas, Liver Cell" OR "Cell Carcinoma, Liver" OR "Cell Carcinomas, Liver" OR "Liver Cell Carcinomas" OR "Hepatocellular Carcinoma" OR "Hepatoma" OR "Hepatomas", and 2) quality of life: "Life Quality" OR "Health-Related Quality Of Life" OR "Health Related Quality Of Life" OR "HRQOL". We then used the same terms to conduct cross-validation searches with Cochrane Library, PsychINFO, and Embase.

Inclusion Criteria and Study Selection

All observational and interventional studies were included if they included HRQoL results, either as an exposure or an outcome. Studies were also included if they included HRQoL as a secondary outcome. Exclusion criteria were as follows: 1) a literature review, commentary, or case study article; 2) studies with samples including children or adolescents only; 3) studies with samples involving heterogeneous populations diagnosed with other cancers or other liver disease; and 4) studies reporting findings not directly relevant to the core concept of HRQoL (Fig. 1).

Data Collection Process

We developed a data extraction sheet, performed a pilot-tested using five randomly selected studies from our search results, and refined it accordingly. Two review authors independently extracted data from the included studies and then discussed the results. Disagreements were resolved by discussion until a consensus was reached between the two review authors. We extracted the data depending on whether HRQoL was measured as an exposure or an outcome. If no agreement could be reached, a senior author (JC) would final decision. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as a guide to ensure that current standards for systematic review methodology were met (18).

Data Items

The following information and data were extracted from each included study: 1) purpose of assessing HRQoL (exposure or outcome); 2) study design (cross-sectional, cohort, or interventional) and methods (quantitative, qualitative, or mixed); 3) characteristics of the study such as nation, author, year of publication, year the study began, and tool used to measure HRQoL; 4) characteristics

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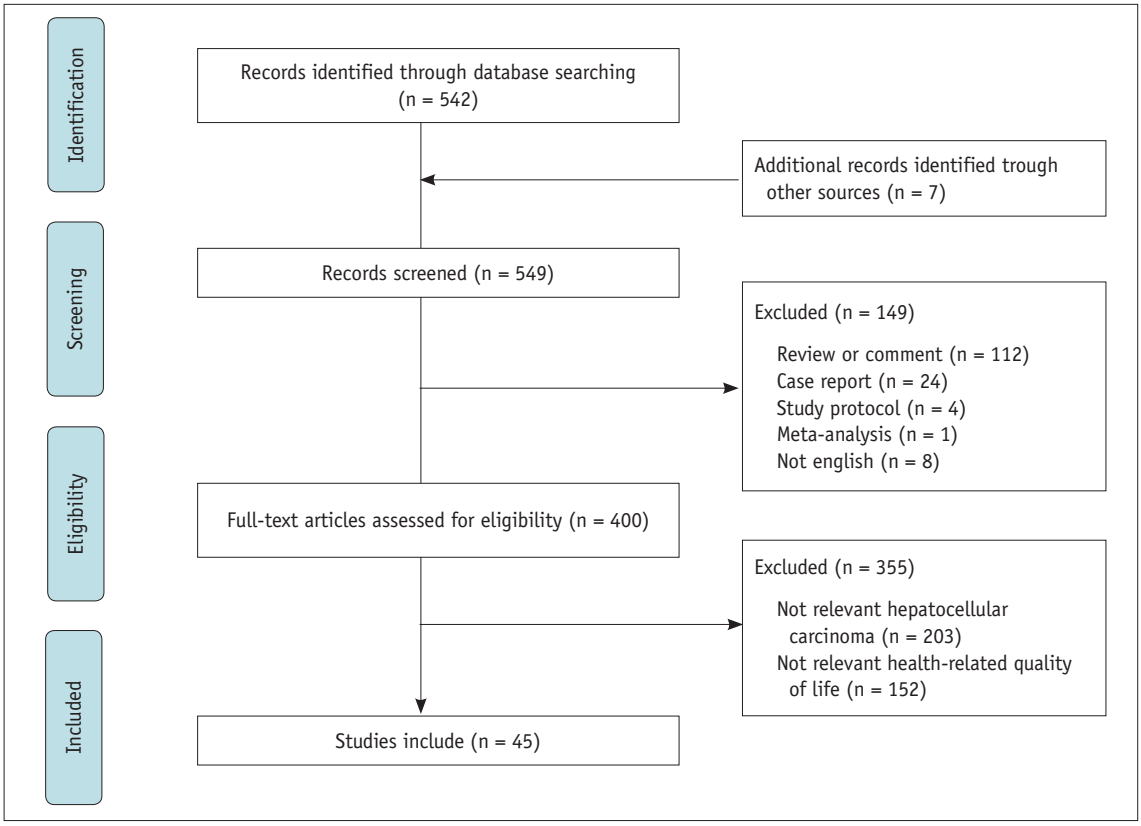

Fig. 1. Flow diagram of study selection.

of participants such as number of participants included, mean age, mean survival at enrollment, stage, liver function, and patient treatment status at enrollment; and 5) summary of main results. Since studies assessing the HRQoL in HCC patients were heterogeneous in purpose and methodology, we did not use summary measures such as risk ratio or difference in means.

Risk of Bias in Individual Studies

If the study was not a randomized controlled trial, we evaluated the risk of bias in individual studies among those that used HRQoL as primary exposure or outcome. To evaluate the risk of bias, we used Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I). This tool can be used to evaluate the effects of exposure on observational studies—such as cohort studies and case control studies—in which exposed groups are allocated during the course of normal treatment decisions, and quasi-randomized studies in which the method of allocation falls short of full randomization (19). ROBINS-I detected bias due to confounders, bias in participant selection, bias in classifying interventions (or exposure), bias due to deviations from intended interventions, bias due to missing data, bias in measuring outcomes, bias in selecting reported results, and overall risk of bias. We classified risk of bias as low, moderate, serious, critical risk of bias, and no information.

To explore variability in study results (heterogeneity), we specified the following hypotheses before conducting the analysis. We hypothesized that the effect size might differ according to the methodological quality of studies. We did not evaluate risk of bias across studies due to heterogeneous study objectives.

RESULTS

Study Selection

In our PubMed search, we found 542 relevant studies conducted during the study period (2009–2018). When we performed a search using the same research terms in Embase, PsycINFO, and Cochrane Library, we found 7 additional articles, resulting in 549 studies. We excluded 149 studies due to their study design (Fig. 1). Reviews or comments (n = 112), case reports (n = 24), study protocols

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(n = 4), and meta-analysis (n = 1) were also excluded. An additional eight papers were excluded as they were written in other languages. Next, we reviewed the remaining 400 eligible studies and excluded 355 that were not relevant to HCC (n = 203) or HRQoL (n = 152), resulting in 45 studies which met the inclusion criteria.

Study Characteristics

Among the 45 studies, HRQoL was assessed as an outcome in 40 studies (Table 1) and as an exposure in 5 studies (Table 2). USA (n = 10, 23%) and China (n = 10, 23%) conducted the largest number of HRQoL studies, followed by Japan (n = 5, 12%) and France (n = 4, 9%). Seven (16%) studies were multinational. The mean duration since enrolling patients or collecting data to publish the manuscript was 7.3 years (standard deviation = 3.6 years).

Most studies assessed HRQoL using quantitative methods (n = 42, 93%), with only three using qualitative methods.

Table 1. Summary of Studies that Used HRQoL as Outcomes (n = 40)

Study	Year	Nation	Study Design	n	Mean Age (Median)	Severity	Child-Pugh Score	Status at Enrollment	Type of Treatment	Intervention or Treatment	QoL Questionnaire
Measures of HRQoL in HCC patient (n = 16)											
Wible et al. (29)	2010	USA	Cohort	73	62	All stage	A 34 B 37 C 2	At diagnosis	TACE		SF-36
Qiao et al. (49)	2012	China	Cross sectional	140	52	All stage	A 84 B 29 C 27	At diagnosis	No treatment		FACT-Hep
Hsu et al. (59)	2012	Taiwan	Cross sectional	300	62	All stage	A 202 B 88 C 10	All	Combined		EORTC QLQ-C30
Shun et al. (60)	2012	Taiwan	Cohort	89	61	All stage	A 41 B 42 C 6	After treatment	TACE		SF-12, SDS, HADS
Fan and Eiser (30)	2012	Taiwan	Cross sectional	33	54	All stage	Unknown	After treatment	Resection, TAE/TACE, Chemo -therapy		Interview
Cao et al. (27)	2013	China	Cross sectional	155	53	All stage	A 146 B 9	After treatment	TACE		MDASI and SCL
Fan et al. (61)	2013	Taiwan	Cross sectional	286	60	All stage	A 224 B 42 C 16 Missing 4	After treatment	Resection, TAE/TACE, chemo		EORTC QLQ-C30, Brief IPQ, Jalowiec Coping Scale
Kaiser et al. (28)	2014	USA	Cross sectional	10	58	Advanced-stage	Not mention	All	Systemic therapy		Pain (FACT), EORTC QLQ-HCC18, and interview
Butt et al. (62)	2014	USA	Cohort	83	64	All stage	Mean = 6.1 (1.3)	After treatment	Combined		FACT-Hep, BPI, Interference Scale
Mise et al. (47)	2014	Japan	Cohort	69	69	All stage	Unknown	At diagnosis	Resection		SF-36
Phillips et al. (63)	2015	Multi	Cohort	167	56	Advanced-stage	A 86 B 69 C 24	At diagnosis	No treatment		EORTC QLQ-C30

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Table 1. Summary of Studies that Used HRQoL as Outcomes (n = 40) (Continued)

Study	Year	Nation	Study Design	n	Mean Age (Median)	Severity	Child-Pugh Score	Status at Enrollment	Type of Treatment	Intervention or Treatment	QoL Questionnaire
Lei et al. (39)	2016	China	Cohort	207	47	Early-stage	Unknown	After treatment	Resection or LT		SF-36, SCL-90-R
Hinrichs et al. (64)	2017	Germany	Cohort	79	66	Advanced-stage	A 60 B 19	At diagnosis	TACE		EORTC QLQ-C30, HCC18
Hansen et al. (65)	2017	USA	Cross sectional	18	63	Advanced-stage	Unknown	After treatment	Sorafenib, TACE or radiation		MSAS
Chie et al. (46)	2017	France	Cross sectional	227	61	All stage	A 180 B 40 C 7	After treatment	Resection, RFA, TACE, or systemic treatment		EORTC QLQ-C30, HCC18
Gill et al. (66)	2018	Multi	Cross sectional	256	(64)	All stage	Unknown	After treatment	Combined		Side Effects and QoL (developed)
Treatment efficacy on HRQoL (n = 17)											
Kuroda et al. (45)	2010	Japan	Intervention	35	66	All stage	A 14 B 19 C 2	After treatment	RFA	BCAA	SF-8
Tian et al. (42)	2010	China	Intervention	97	52	Advanced-stage	A 70 B 27	During treatment	Unknown	Chinese medicine therapy	Pain with VAS, Karnofsky's Scores
Chow et al. (44)	2011	Multi	Intervention	185	58	Advanced-stage	A 86 B 69 C 24	At diagnosis	No treatment	MA (320 mg day)	EORTC QLQ-C30
Toro et al. (31)	2012	Italy	Cohort	51	70	All stage	A 28 B 23	At diagnosis	No treatment	Resection, TACE and RFA	FACT-G
Salem et al. (33)	2013	USA	Cohort	56	67	Advanced-stage	A 48 B 8	At diagnosis	No treatment	TACE and ^{90}Y radioembolization	FACT-Hep
Meyer et al. (34)	2013	UK	Intervention	86	63	Advanced-stage	A 71 B 15	At diagnosis	No treatment	TACE and TAE	EORTC QLQ-C30, HCC18, CTCAE
Huang et al. (38)	2014	China	Cohort	348	51	Early-stage	A 348	After treatment	TAE	Resection and RFA	FACT-Hep
Kolligs et al. (35)	2015	Multi	Intervention	28	66	Moderate/late stage	A 25 B 3	At diagnosis	Unknown	SIRT and TACE	FACT-Hep, CTCAE
Xing et al. (26)	2015	USA	Cohort	118	60	Advanced-stage	A 66 B 46 C 6	At diagnosis	No treatment	DEB-TACE	SF-36
Chie et al. (32)	2015	Multi	Cohort	171	62	All stage	A 135 missing 36	At diagnosis	Combined	Resection, RFA, or TACE	EORTC QLQ-C30, HCC18
Anota et al. (36)	2016	France	Intervention	21	64	All stage	A 16 B 5	At diagnosis	Unknown	DEB-TACE (5/10/15 mg)	EORTC QLQ-C30, CTCAE
Kensinger et al. (67)	2016	USA	Cohort	502	54	All stage	Unknown	All	Unknown	LT	SF-36, BAI, CES-D

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Table 1. Summary of Studies that Used HRQoL as Outcomes (n = 40) (Continued)

Study	Year	Nation	Study Design	n	Mean Age (Median)	Severity	Child-Pugh Score	Status at Enrollment	Type of Treatment	Intervention or Treatment	QoL Questionnaire
Lv et al. (43)	2016	China	Intervention	120	52	Advanced-stage	A 73 B 47	At diagnosis	Unknown	TACE with Parecoxib sodium	CTCAE, Pain Score (NRS), Self Developed QoL Items
Qiu et al. (68)	2017	China	Intervention	91	65	Advanced-stage	A 17 B 39 C 35	After treatment	TACE, RFA, TACE + RFA, Sorafenib	TIPS in PVTT patients	Karnofsky's Scores
Aliberti et al. (37)	2017	Italy	Cohort	42	65	Advanced-stage	A 31 B 11	After treatment	Resection, RFA, or chemotherapy	TACE and PEG embolics	Palliative Performance Scale, CTCAE
Chau et al. (69)	2017	Multi	Intervention	565	62	Advanced-stage	A(5/6) 553 7 point = 12	After treatment	Sorafenib therapy	Ramucirumab 8 mg/kg	FHSI-8 and EuroQoL-5D
He et al. (70)	2018	China	Cohort	128	46	Early-stage	A 84 B 35 C 9	After treatment	Resection, RFA, or LT		SF-36
QoL and its associated factors (n = 4)											
Mikoshiba et al. (48)	2013	Japan	Cross sectional	128	69	All stage	A 96 B/C 32	After treatment	Unknown		EORTC QLQ-C30, HCC18, CES-D
Hansen et al. (52)	2015	USA	Cohort	45	62	Advanced-stage	Unknown	After treatment	Any treatment		Interview
Shomura et al. (41)	2016	Japan	Cohort	54	(71)	Advanced-stage	Score of 5 = 33, Higher than 5 point = 27	After treatment	Sorafenib		SF-36
Jie et al. (51)	2016	China	Cohort	218	50	All stage	Unknown	At diagnosis	Unknown	Resection or RFA	EORTC QLQ-C30, Brief IPQ
Validation (n = 3)											
Mikoshiba et al. (53)	2012	Japan	Cross sectional	192	68	All stage	A 127 B 53 C 12	All	Combined		EORTC QLQ-C30, QLQ-HCC18
Chie et al. (55)	2012	Multi	Cross sectional	227	61	All stage	A 180 B 38 C 2	After treatment	Combined		EORTC QLQ -C30, EORTC QLQ -HCC18
Yang et al. (54)	2015	China	Cross sectional	114	51	All stage	Unknown	All	Resection or others		EORTC QLQ-C30

BAI = Beck Anxiety Inventory, BCAA = branched-chain amino acid-enriched nutrient, BPI = Brief Pain Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, CTCAE = Common Terminology Criteria for Adverse Events, DEB = doxorubicin drug-eluting bead, EORTC = European Organization for Research and Treatment of Cancer, EORTC QLQ-C30 = EORTC Quality of Life Questionnaire Core 30, FACT = Functional Assessment of Cancer Therapy, FACT-G = FACT-General, FACT-Hep = FACT-Hepatobiliary, FHSI-8 = FACT Hepatobiliary Symptom Indexes, HADS = Hospital Anxiety and Depression Scale, HCC = hepatocellular carcinoma, HRQoL = Health-Related QoL, IPQ = Illness Perception Questionnaire, LT = liver transplantation, MA = megestrol acetate, MDASI = M. D. Anderson Symptom Inventory, MSAS = Memorial Symptom Assessment Scale, NRS = Numeral Rating Scale, PEG = polyethylene glycol, PVTT = portal vein tumor thrombus, QoL = quality of life, RFA = radio-frequency ablation, SCL = symptom checklist, SDS = Symptom Distress Scale, SF = short form, SIRT = selective internal radiation therapy, TACE = transarterial chemoembolization, TAE = transarterial embolization, TIPS = transjugular intrahepatic portosystemic shunt, VAS = visual analogue scale

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Table 2. Summary of Studies that Used HRQoL as Exposure (n = 5)

Author	Year	Nation	Study Design	n	Mean Age (Median)	Time at Enroll	Severity	Child-Pugh Score	QoL Measurement	Number of QoL Assessments	Primary Outcome
Diouf et al. (56)	2013	France	Cohort	271	67	At diagnosis	Late-stage	A 182 B 64 C 2 D 23	EORTC QLQ-C30	1	OS
Diouf et al. (58)	2015	France	Cohort	271	67	At diagnosis	Late-stage	A 182 B 64 C 2 D 23	EORTC QLQ-C30	1	OS
Meier et al. (50)	2015	USA	Cohort	130	57	At diagnosis	All	A 56 B 45 C 29	EORTC QLQ-C30, HCC18	1	OS
Li et al. (57)	2017	Hong Kong	Cohort	472	(60)	After treatment	Hetero	A 319 B 130 C 23	EORTC QLQ-C30, HCC18	1	OS
Xing et al. (71)	2018	USA	Cohort	30	62	At diagnosis	Late-stage	A 20 B 10	SF-36	4	OS

OS = overall survival

There were 23 (51%), 13 (29%), and 9 (20%) cohort, cross-sectional, and interventional studies, respectively. With cohort and interventional studies, the median follow-up time was 21 months, and on average, HRQoL was assessed three times during the follow-up.

Among 23 cohort studies, 8 (35%) evaluated the effects of specific HCC treatments on HRQoL, and 7 (30%) evaluated the HRQoL of HCC patients over time. Three cohort studies aimed to identify factors associated with HRQoL (13%), and five cohort studies evaluated the impact of HRQoL on the clinical outcome (22%). Among the 14 cross-sectional studies, 9 evaluated the HRQoL at a certain point in time, and 3 were tool validation studies. All intervention studies (n = 9) evaluated the effect of treatment on HRQoL.

HRQoL Measurements

Eight studies used the short form (SF)-36, which is a general measurement tool for assessing HRQoL (20). Half of the studies (n = 25, 56%) used cancer specific HRQoL questionnaires. The most frequently used questionnaire was the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) (n = 17) (21), followed by the Functional Assessment of Cancer Therapy-General (FACT-G) (n = 6) (22). In addition, 38 studies used additional liver cancer-specific questionnaires. The most frequently used liver cancer-specific questionnaires were the EORTC-hepatocellular carcinoma 18 (HCC18) (23) and the FACT-Hepatobiliary (FACT-Hep) questionnaires (24). One study used the FACT Hepatobiliary Symptom Index-8 (FHSI-8), which is an eight-item subset of FACT-Hep, to assess specific symptoms of hepatobiliary carcinoma (25).

Participants

The median sample size was 154 (range, 15–565) participants, and the median age of the study participants was 58.9 years. In total, 18 (40%), 19 (42%), and one (2%) studies were conducted with patients before (at diagnosis), after, and during HCC treatment, respectively. Seven (16%) studies recruited patients at different treatment stages. While 18 studies (40%) assessed the HRQoL of late-stage HCC patients, only 3 studies evaluated the HRQoL of early-stage HCC patients. Similarly, 19 (42%) and 14 studies (31%) were conducted in patients who had a Child-Pugh score of more than C, and A, or B, respectively.

HRQoL as Outcomes

Among 40 studies, which assessed HRQoL as an outcome (Table 1), 16 studies evaluated the HRQoL of HCC patients, and of those, 8 focused on TACE patients and four on resection patients. According to SF-36 scores, when compared to the age- adjusted healthy US population, patients with HCC prior to initiation had lower general health (38.2 vs. 70.1), mental health (45.2 vs. 75.2), physical functioning (36.2 vs. 83.0), role–emotional (37.7 vs. 77.9), role–physical (37.7 vs. 77.9), social functioning

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(38.7 vs. 83.6), and vitality (42.1 vs. 57.0) (26). Patients commonly reported abdominal pain, nausea, jaundice, weight loss, and body image issues. Among late stage HCC patients, the most severe symptoms at diagnosis were fatigue and distress (27), and 90% of patients reported pain during and after treatment (28). The abdomen and lower back were the most common sites of pain (28). Fatigue was the most serious symptom followed by sleep disturbance, distress, sadness, and lack of appetite even after treatment (27). Symptoms of upper gastrointestinal distress and liver function impairment also remained after treatment (27). However, patients exhibited improved mental health scores after the treatment compared to before treatment (29). According to the results of a qualitative study, patients perceived HCC as a long-term and chronic disease that, while incurable, might be controllable. Control measures included focusing on managing HCC and its symptoms, managing emotional responses, and leading a normal life (30).

HRQoL in Patients Treated with TACE

Seventeen studies compared the effects of treatment methods on the HRQoL. Among them, 7 studies evaluated the HRQoL of TACE patients, and other studies compared the HRQoL of TACE patients to those treated with RFA or resection (n = 2) (31, 32), ^{90}Y therapy, (n = 1) (33), transarterial embolization (n = 1) (34), and/or selective internal radiation therapy (n = 1) (35). Three studies assessed HRQoL by different methods or dose of TACE: doxorubicin drug eluting bead (DEB)-TACE therapies (n = 2) (26), maximum tolerated dose of TACE (n = 1) (36), or TACE using loaded polyethylene glycol (PEG) drug-elutable microspheres (n = 1) (37). Patients treated with TACE had lower baseline scores in all eight HRQoL domains of the SF-36 compared to the US age-adjusted healthy normal participants. The HRQoL post therapy and at 6 or 12 months after completion of TACE did not differ between patients receiving ≥ 4 vs. ≤ 3 DEB-TACE (p > 0.05) (26). Prior to TACE treatment, the 5 most severe symptoms ranked in order were fatigue, distress, sadness, sleep disturbance, and lack of appetite (27). After TACE, fatigue was still the most bothersome symptom, followed by sleep disturbance, distress, sadness, and lack of appetite (27). After TACE, while bodily pain scores improved, vitality scores worsened, which is associated with fatigue (29). Mental health scores improved after 4 months of TACE. However, at 12 and 24 months after treatment, patients continued reporting decreased physical (12 months: -34.29, 24 months: -40.99), social/family (12 months: -35.32, 24 months: -42.27), emotional (12 months: -28.06, 24 months: -37.35), and functional (12 months: -43.07, 24 months: -53.61) well-being (31).

HRQoL in Patients Treated by Resection

The HRQoL of resection patients was compared to that of patients treated with RFA (n = 2) (32, 38), transplantation. (n = 1) (39), or both (n = 1) (40). Patients with liver transplantation or resection had a relatively better HRQoL compared to patients with other treatments (39). After hepatic resection, HRQoL first declined, but then increased to preoperative levels at 6 months after surgery, and slightly improved than preoperative levels at 12 months after surgery (38). Physical, social/family, emotional, and functional well-being of patients treated by hepatic resection were significantly better than for all other treatments at 24 months after resection (31).

HRQoL in Patients Treated with RFA

According to FACT scores, physical, social/family, emotional, and functional well-being declined following RFA treatment, and did not recover to preoperative levels at 24 months after surgery (31). Additionally at 24 months after surgery, changes in physical (RFA: -18.81, surgery: 7.37), social/family (RFA: -24.29, surgery: 7.13), emotional (RFA: -29.98, surgery: 6.73), and functional (RFA: -18.35, surgery: 6.05) well-being before and after RFA treatment were poorer than that of surgery patients (31). However, RFA patients had less bodily pain (RFA: 87.9 vs. transplantation: 80.2 vs. surgery: 80.5, p = 0.01) and more vitality (RFA: 81.9 vs. transplantation: 72.4 vs. surgery: 73.4, p < 0.01) than patients with transplantation or resection at 3 years after treatment (40). Patients treated with RFA reported better physical, social/family, emotional, and functional well-being at 24 months after treatment than patients treated with TACE (31).

HRQoL in Patients Treated with Targeted Therapy (Sorafenib)

Patients receiving sorafenib experienced hand-foot skin reactions, diarrhea, or weight loss. Sorafenib use was associated with deterioration of liver function, and the progressive nature of the disease limited the efficacy of sorafenib. During treatment, symptoms did not improve, and patients experienced decreased physical functioning and vitality over time (41).

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Effects of Supportive Care Intervention on the HRQoL

Four studies evaluated the effects of supportive care/intervention on the HRQoL, and all studies were conducted with inoperative or advanced stage HCC patients. Chinese medicine comprehensive therapy (42) and perioperative parecoxib sodium (43) were used for pain relief, and megestrol acetate (MA) (44) and branched-chain amino acid (BCAA)-enriched nutrients (45) were used for nutrition support. Chinese medicine and perioperative parecoxib sodium improved pain scores. Supplementation with BCAA-enriched nutrients for one year showed improved nutrition and HRQoL among patients with inoperable HCC undergoing TACE (45). MA helped alleviate appetite loss and nausea/vomiting in patients with treatment-naïve advanced HCC compared to patients without MA, but demonstrated no role in prolonging overall survival (44).

Factors Associated with HRQoL

Four studies were conducted to identify factors that affected HRQoL among HCC patients. In terms of patient characteristics, being Asian (46), being female (47), living alone (48), and unemployment (48) were associated with poor HRQoL. Regarding clinical characteristics, severe TNM stage (49), Barcelona Clinic Liver Cancer tumor stage (50), and cirrhosis were associated with poor HRQoL. Other physical (fatigue, sleep disturbance, and lack of appetite) (27) and emotional symptoms (distress, sadness, and depression) were significantly associated with poor HRQoL (27, 48). In terms of social function, disclosure of cancer (51) and lack of information were related to worse HRQoL (52). In addition, illness perceptions and personal control of the patients' own disease were positively correlated with HRQoL (51).

HRQoL Tool Validation Studies

Three Japanese- and Chinese-language studies were conducted to validate the EORTC QLQ-HCC18. Besides two validation studies for the Japanese (53) and Chinese EORTC QLQ-HCC18 (54), one study was conducted for cross-cultural validation (55). Cronbach's α was used to measure internal consistency, showing a value greater than 0.60 in the Japanese and Chinese EORTC QLQ-HCC18. In the international field validation study, researchers found that there were low or moderate correlations between the QLQ-HCC18 and QLQ-C30. As a result, they recommended the use of EORTC QLQ-HCC18 as a supplementary module for the EORTC QLQ-C30 in clinical trials for patients with HCC.

HRQoL as an Exposure

Five studies measured HRQoL as an exposure (Table 2). Poor HRQoL is an independent prognostic factor of all-cause mortality in palliative HCC patients (56). In addition, experiencing pain, fatigue, poor physical functioning (57), and poor role functioning (50) were shown to be independent factors associated with mortality. Based on the EORTC QLQ-C30, 50 points out of 100 was the optimal cutoff value to predict mortality among HCC patients for global health, 58.3 for physical functioning, 66.7 for role functioning, 66.7 for fatigue, and 33.33 for diarrhea (58).

Risk of Bias

Among studies primarily designed to measure HRQoL, 15 showed a moderate risk of bias, 13 showed a critical risk, and 3 showed a serious risk (Fig. 2). Confounding factors were identified as the most frequent critical or serious risk (11/31). Almost 30% of studies did not control for confounding factors (Fig. 2).

DISCUSSION

This review summarized 45 studies measuring the HRQoL of HCC patients, published between 2009 and 2018. During this period, USA and China conducted the largest number of HRQoL studies, followed by Japan and France. Approximately half of the studies were cohort studies, and one-fifth were intervention studies. In the cohort and interventional studies, the median follow-up time was 21 months, and on average, HRQoL was assessed three times during follow-up. Most studies assessed HRQoL as an outcome and evaluated or compared the HRQoL of HCC patients depending on type of treatment or stage of disease. HCC patients had a worse HRQoL than the general population, including those with early-stage HCC. Patients commonly experienced pain, fatigue, sleep disturbance, distress, and lack of appetite, and these symptoms remained problematic even a few years after treatment. TNM stage, tumor stage, presence of cirrhosis, being Asian, being female, living alone, or being unemployed were associated with poor HRQoL. Additional physical and emotional symptoms were associated with poor HRQoL, and poor HRQoL was an independent prognostic factor of all-cause mortality among advanced stage HCC patients. Despite this significance, only four interventional studies tried to improve the HRQoL in HCC patients.

This review is consistent with previous reviews (15-17) which showed that HCC patients (including early-

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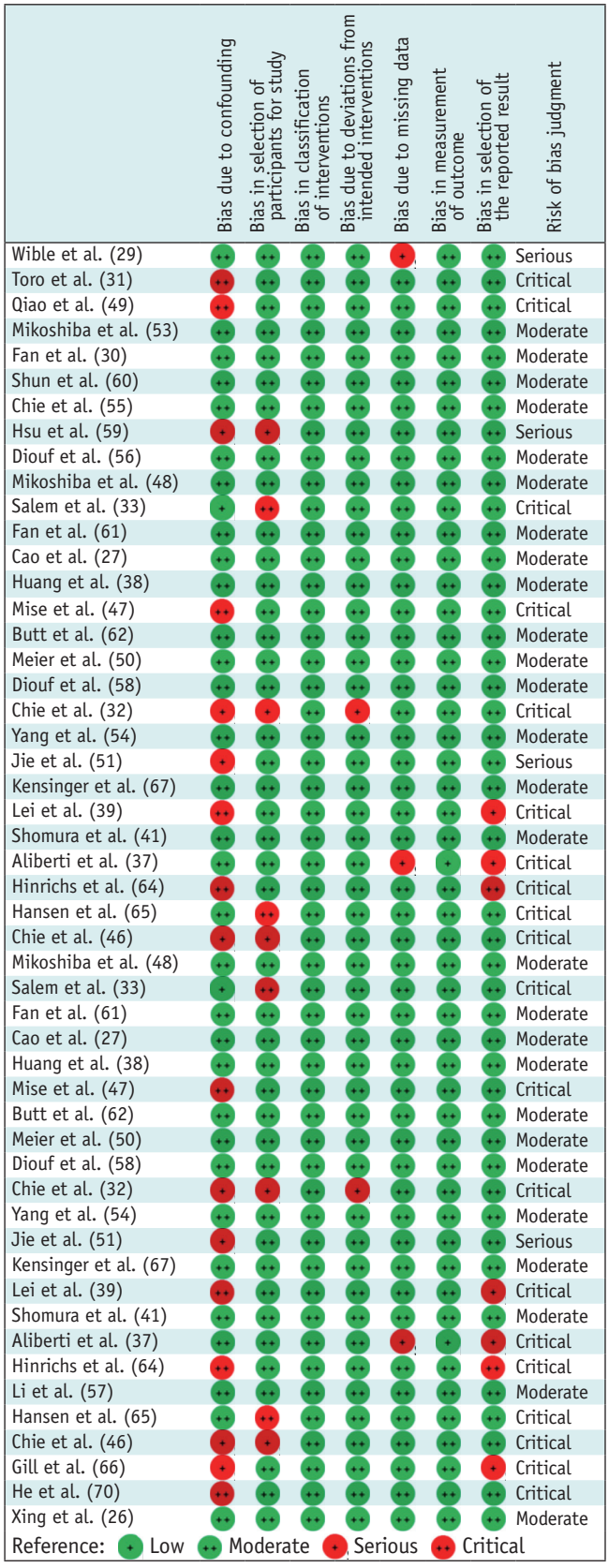

Fig. 2. Evaluated risk of bias for non-randomized controlled trial study with health-related quality of life as primary exposure or outcome (n = 31).

stage) have a worse HRQoL in terms of physical function, emotional status, and functional ability than the general population. HCC patients commonly experienced fatigue, sleep disturbance, distress, sadness, and lack of appetite regardless of disease stage or course of treatment. In terms of liver specific problems, patients reported abdominal pain, nausea, jaundice, weight loss, and body image issues. In general, after treatment completion, the HRQoL of HCC patients improved over time, though results varied based on treatment type and stage at diagnosis. For example, the HRQoL of patients who underwent resection improved over time (comparable to levels before treatment), but the HRQoL of patients treated with TACE did not improve, even several years after treatment completion. While there were a limited number of studies directly comparing HRQoL by treatment method, patients treated by resection/surgery or RFA (with small size tumor) seemed to have a better HRQoL than patients treated with TACE. This might be because patients with early stage HCC were more likely to receive surgery or RFA rather than TACE, and patients with TACE likely had a worse HRQoL at diagnosis compared to patients treated with other methods.

According to previous reviews, few studies focused on assessing the HRQoL of HCC patients and most were conducted in a palliative setting (16). However, in our analysis, we found an increasing number of studies evaluating HRQoL of HCC patients, including several conducted with early or intermittent stage patients. Additionally, studies evaluated and compared HRQoL based on new treatment modalities such as RFA, TACE, and sorafenib. We found that RFA patients had decreasing social/family, emotional, and long-term physical well-being. TACE patients had a worse HRQoL during and after treatment compared to RFA patients. While some studies evaluated the HRQoL 2 or 3 years after treatment, a limited number included long-term survivors, and no study primarily focused on this group. This might be due to the relatively high mortality in liver cancer patients, with health professionals focusing more on the HRQoL of patients under active treatment rather than long-term survivors. Lastly, our review included qualitative studies, which indicated that patients perceived HCC as a long-term difficulty, with challenges that include symptom management, emotional response management, and generally trying to lead a normal life.

Several limitations of this review should be acknowledged. First, we specifically focused on studies conducted with HCC-only patients; we neglected studies that included

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subjects with metastasis or those diagnosed with other types of liver cancer. Secondly, because we found HRQoL studies using the search term 'quality of life,' we might have missed studies using other terminology or expressions. However, we attempted to identify articles using key words similar to the MeSH terms. Thirdly, since the purpose of this review was to analyze all types of studies on HRQoL, studies included in this review were heterogeneous in purpose and design, and we were unable to conduct a quantitative review. Furthermore, we evaluated the quality of the reviewed studies by identifying potential bias.

In summary, from 2009 to 2018, an increasing number of studies evaluated the HRQoL of HCC patients, with studies becoming more diverse by covering a wider patient population (patients at different stage of disease), various topics (different treatment effects on HRQoL, effect of HRQoL on survivorship and psychosocial well-being), and different study designs (cohort and interventions). Regardless of stage at diagnosis or treatment method, HCC patients experienced various physical and psychosocial symptoms resulting in poor HRQoL and worse progression of the disease, yet there were limited supportive interventions. Given the increase in HCC cases and HCC survivors, more attention is needed to evaluate and improve the HRQoL of HCC patients.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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