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REVIEW

A closer look at quality of life in the hepatocellular carcinoma literature

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Abstract

Purpose Adults with hepatocellular carcinoma (HCC) have a high symptom burden. Their quality of life (QOL) has been shown to be significantly impacted by both the disease and its treatment, adding to the high symptom burden that these patients experience. The primary aims of this paper are as follows: (1) to identify how QOL is being defined in HCC literature and (2) to identify how QOL is being measured in the HCC literature using Ferrell's model of QOL.

Methods A systematic review was completed of relevant studies published after 2014, using PubMed, CINHAL, and PsycInfo. Relevant studies were reviewed by 2 reviewers using PRISMA guidelines.

Results From a total of 1312 papers obtained in the initial database search, 30 met inclusion criteria and are included in this review. From the included articles, 10% included a definition of QOL and 3% addressed the spiritual domain of QOL. Majority of study participants were in the early stage of HCC, though the majority of adults with HCC are diagnosed in the advanced stage. Only 3% of included studies included greater than 22% population of advanced stage of HCC.

Conclusion The results of this systematic review demonstrate the need for future research into QOL in the advanced stage of QOL. It also identified gap in the literature concerning the definition of QOL in HCC and the spiritual domain of QOL in HCC.

Keywords Quality of life · Hepatocellular carcinoma · Systematic review · Liver cancer · Health-related quality of life · Ferrell model of quality of life

Introduction

Liver cancer is the sixth most common cancer and the fourth leading cause of cancer-related deaths worldwide, with hepatocellular carcinoma (HCC) making up 80% of all liver cancers [1–3]. The highest incidence of liver cancer is seen in Asia which makes up an estimated 75% of the world's liver cancer burden. In the USA (USA), which has one of the lowest incidences of liver cancer in the world, HCC is the fifth highest cancer-related death for men, and ninth highest for women, with a 5-year survival rate of only 18% [1, 4, 5]. While the death rate in most cancers is decreasing, HCC cancer deaths are increasing in the USA and worldwide [1, 4]. This increase may be largely due to the parallel increased incidence of hepatitis and liver cirrhosis, the primary etiologies of HCC [1, 2].

Approximately 44% of adults with HCC are diagnosed when the disease is localized to the liver alone and still has available curative options, such as liver transplant [6]; the majority(56%) are diagnosed in the advanced stages of the disease, when a cure is no longer an option [6, 7]. All adults have a high symptom burden as symptoms of HCC can coexist with those of severe hepatic dysfunction such as: abdominal pain, hypoglycemia, diarrhea, nausea, vomiting, jaundice, cholangitis, fever, and peritonitis [5, 8]. Adults with HCC also frequently suffer from hepatic encephalopathy, further adding to the already high symptom burden of HCC [2, 8, 9]. Due to the high symptom burden and mortality for adults with HCC, ensuring optimal quality of life (QOL) should be in the forefront of care efforts.

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Quality of life (QOL)

QOL is a multifaceted concept that embodies all aspects of a person's life. It is a dynamic as opposed to static process, dependent on individual perceptions and experiences and varying greatly within and across the human lifespan [10]. QOL has been described and defined in a variety of ways, including as a global, holistic view compared with a more focused examining of a portion of the human experience such as individual welfare, social, and/or psychological QOL [11]. For this review, QOL was viewed as an overarching concept that includes all aspects of being [12]. Within these parameters, Felce and Perry (1995) define QOL as a combination of life conditions and satisfaction weighted by their importance based on personal values [11]. The World Health Organization (WHO) defines QOL as more than simply the absence of disease, but as "a state of complete physical, mental, and social well-being" [13]. The definition of QOL presented in Ferrell's model of QOL, specific to those who have been diagnosed with cancer, is that QOL is a personal sense of well-being and embodies physical, psychological, social, and spiritual domains. Though all of these definitions have slight variations concerning the specific domains of QOL, the key elements that they share is that QOL is an overarching term used to describe the wholeness of the human experience, and that the definition of QOL comes back to the individual. One key finding that all definitions of QOL have in common is that QOL is determined by the individual's experience. QOL is a vital metric when considering patient outcomes in both clinical care and research.

Just as there are many definitions of QOL, multiple theoretical and conceptual frameworks and models have been established to examine and describe the concept of QOL [14]. Ware's (1984) framework included the basic well-being concepts of physiologic statue, physical function, mental health and social well-being, but also recognized the role of concepts such as finance, housing, and employment on overall QOL [15]. Patrick and Bergner (1990) present a causal model examining the impact of impairment due to disease on functioning which directly affects perceptions of health, all of which is impacted by environment [16]. Wilson and Cleary's (1995) model explore the impact of not only medical, but non-medical factors on overall QOL with the key concepts of biological factors, symptoms, functional status, and perceptions of health [17]. All of these frameworks explore QOL in the disease process, but QOL is not limited by disease. The frameworks of Read et al. (1987) explores QOL outside of the disease process. Read et al. (1987) included the key concepts of environment, personal characteristics, and health problems to evaluate overall health without a distinction between health and QOL [18].

Though many of these models and frameworks were developed with a lens on the disease process, none of them encompass the disease-specific needs of adults facing cancer. Ferrell's (1996) model of QOL was specifically developed to examine QOL in the cancer populations. In cancer research, Ferrell's (1996) model of QOL in cancer survivors defines the four domains, physical, psychological, social, and spiritual well-being, that impact QOL (Fig. 1) [19]. Each of the domains plays a vital role in determining the overall QOL and well-being of all adults living with cancer, including HCC. Both generic QOL measurement tools, along with liver/HCC disease-specific measurement tools, have been developed in order to capture a comprehensive evaluation of QOL. Evaluating the use of these measurement tools is needed in order to appropriately and accurately determine how overall QOL is addressed in the HCC population, as well as its four sub-domains. As with the other frameworks discussed, Ferrell's model address aspects of physical,

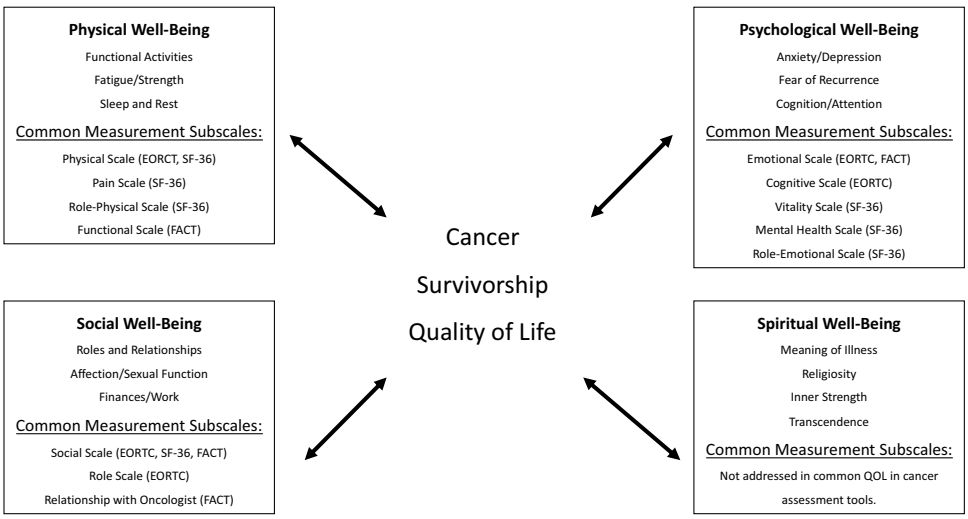

Fig. 1 Conceptual Model of QOL in Cancer [19]

psychological, and social well-being and functioning, but also takes into consideration the impact of spirituality on QOL. Spiritual well-being is a vital concept when examining QOL in the cancer population, and particularly in adults with HCC due to the high mortality rate of this disease.

In adults with HCC, QOL has been shown to be significantly impacted by both the disease and its treatment, adding to the high symptom burden that these patients experience [20–22]. However, it is not well understood *how* QOL is defined, or *how* QOL is being measured in this population. Due to these gaps in understanding, along with an increase in the incidence and mortality of HCC in the USA and worldwide, the primary aims of this paper are to: (1) identify how QOL is being defined in HCC literature, and (2) identify how QOL is being measured in the HCC literature using Ferrell's model of QOL. To address these aims, a systematic review of the literature was undertaken.

Methods

For this review, two investigators performed a search of three electronic databases (CINAHL, PubMed, PsycINFO) using the search terms "quality of life" (OR "QOL" OR "HRQOL" OR "health related quality of life") AND "hepatocellular carcinoma". The search term "hepatocellular carcinoma" was used (rather than the generic "liver cancer") because 80% of adults diagnosed with liver cancer have HCC. Search results were imported into Rayyan, a web-based systematic review application, and duplicates were removed [23]. The reviewers then independently reviewed titles and abstracts of articles and identified those to be included, based on the following criteria: (1) quantitative methodology, (2) data-based original research, (3) participants with exclusively HCC patients or with results for patients with HCC separated from results from patients with other diagnoses in papers with mixed samples, (4) published within the previous 15 years, and (5) available in English. Case studies, narrative reviews, commentaries, letters, non-patient-reported metrics (i.e., Karnofsky Performance Status), or validation of measures studies were excluded.

Full articles were then obtained and reviewed. After both reviewers had completed independent, blinded reviews, Rayyan was unblinded and 100% consensus of articles that met inclusion criteria was reached (Fig. 2). Data extraction was then conducted. Extraction categories included: (1) participant demographics; (2) geographical location of participants; (3) participant disease stage; (4) QOL definition; (5) QOL measurement tool; (6) inclusion of the four domains of QOL (i.e., physical, psychological, social, spiritual), and (7) disease-specific measurements. Extraction categories were directed by Ferrell's (1996) model, specifically the inclusion of the four domains of QOL set in the model. The Ferrell model was chosen because it was developed based on research in cancer to specifically evaluate the QOL needs of cancer survivors. Ferrell's model further guided the reporting of the results based on the four domains of QOL and also the discussion as physical, psychological, social, and spiritual well-being and functioning as vital elements when researching and discussing QOL in the HCC population.

Results

A total of 30 quantitative studies met inclusion criteria (Table 1).

Demographics

Sample size for included studies ranged from 21 to 538 participants with HCC ($M = 180$) for a total of 5583 participants included in this review. The average age of study participants per study ranged from 49 to 71 years ($M = 62$). As HCC is more commonly diagnosed in males rather than females, with an estimated proportion of 75% male worldwide [1], the studies in this review aligned with the global gender distribution of HCC ($M = 82\%$ male; Range 68–100% male). This finding does, however, create a gap in our understanding regarding the female perspective of QOL in HCC, which may be significantly overshadowed and/or uniquely different.

Geographic location

Of the 30 studies, 17 (57%) included participants from Asia, 7 (23%) from Europe, and 6 (20%) from North America. Gill et al. (2018) included participants from 13 countries across North and South America, Europe, Asia, and Australia. None of the studies included participants from Africa.

Disease stage

For our review, the Child–Pugh score (CPS) was used to describe disease stage. CPS is used to assess prognosis in liver disease by scoring total bilirubin, serum albumin, prothrombin time, international normalized ratio, ascites, and hepatic encephalopathy [24]. Total scores are graded as class A, B, or C with a corresponding prognostic survival for one- and two-year survival as: 100% and 85% for class A, 80% and 60% for class B, and 45% and 35% for class C [24]. Of the 30 included studies, 20 (67%) provided description of participants CPS and 6 (32%) studies included an exclusive participants of class A and B. Only two studies (10%) included participants of more than 50% class A, while three (16%) studies had participants with a greater than 80% class A. Of the 14 (70%) studies that included participants in class C, only one (5%) study included more than 22% of

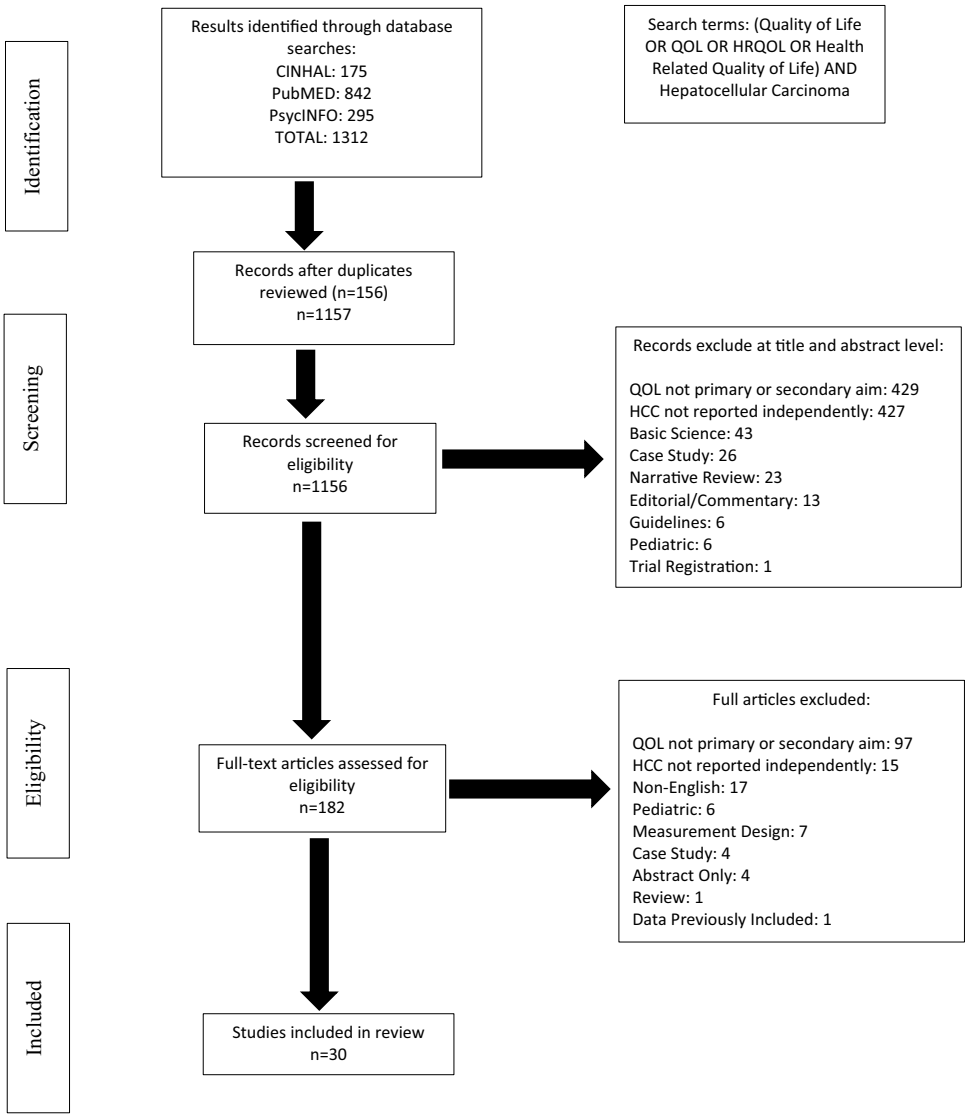

Fig. 2 Flow diagram of the literature review

class C. Of note was Bonnetain et al. (2008), who included exclusively participants with class C, found that QOL was an independent prognostic factor for survival in adults with end-stage HCC.

QOL definition

In Ferrell's (1996) model of QOL, QOL is defined as, "a personal sense of well-being encompassing physical, psychological, social, and spiritual dimensions" (p. 915). A clear definition of QOL was provided in only 3 (10%) of the reviewed articles. Fan et al. (2012) introduced QOL as a broad concept that included the domains of physical, psychological, and social well-being. They further defined QOL as an "integrative index" merging objective functioning and subjective well-being. Phillips et al. (2015) defined QOL as, "Patient's perceptions of their well-being in various areas such as physical, psychological, social, financial, and somatic" (p. 895). Finally, Steel et al. (2005) based their definition of QOL on the WHO definition that QOL is the subject's perception of their lives in the context of their environment, in relation to their goals and expectations. The remaining 27 articles did not offer a definition for the term QOL.

QOL measurement tool

The large majority $n = 28$; 93% of the studies used a validated, reliable measurement tool for QOL. The most commonly used ($n = 14$; 47%) tool was the *European Organization for Research and Treatment of Cancer* (EORTC). The *Functional Assessment in Cancer Treatment* (FACT) was used in 10 (33%) studies, while the *Medical Outcomes Short Form 36* (SF-36), or the *Medical Outcomes Short Form 8*

Table 1 Characteristics of the included studies

References	Location	QOL definition	QOL measure	Disease stage	Sample size	Sample demographics
Bianchi, G., Loguercio, C. et al. (2003) [35]	Europe	Not provided	SF-36	Child–Pugh A 35% B 43% C 22%	101	Mean Age 66 Males 74%
Bonnetain, F., Paoletti, X. et al. (2008) [36]	Europe	Not provided	EORTC QLQ-C30	Child–Pugh C 100%	538	Age ≥ 65: 63% Male 88%
Chie, W.C., Blazeby, J.M. et al. (2017) [37]	Europe Asia	Not provided	EORTC QLQ-C30	Child–Pugh A 79% B/C 18% Missing 3%	227	Mean Age 62 Male 76%
Diouf, M., Filleron, T, (2013) [38]	Europe	Not provided	EORTC QLQ-C30	Child–Pugh A 67% B 24% C 1% D 8%	271	Age ≥ 65: 66% Male 75%
Fan, S., Eiser, C. et al. (2013) [39]	Asia	Provided	EORTC QLQ-C30	Child–Pugh A 78% B 15% C 6% Missing 1%	286	Mean Age 60 Male 76%
Gill, J., Baiceanu, A. et al. (2018) [40]	International	Not provided	Patient reported: 'excellent', 'good', or 'poor' to describe their QOL	Unknown	256	Age ≥ 60: 66% Male 70%
Gmür, A., Kolly, P. et al. (2018) [41]	Europe	Not provided	FACT	Child–Pugh A 67% B 29% C 4%	242	Median Age 64 Male 85%
Hsu, W., Tsai, A. et al. (2012) [42]	Asia	Not provided	EORTC QLQ-C30	Child–Pugh A 67% B 29% C 4%	300	Age ≥ 65: 44% Male 80%
Jie, B., Qiu, Y. et al. (2015) [43]	Asia	Not provided	EORTC QLQ-C30	Qualify for curative treatment	218	Mean Age 50 Male 86%
Kim, G., Kim, H. et al. (2019) [44]	Asia	Not provided	EORTC QLQ-C30 FACT	Child–Pugh A 91% B 9%	300	Mean Age 55 Male 88%
Kondo, Y., Yoshida, H. et al. (2007) [45]	Asia	Not provided	SF-36	Child–Pugh A/B 100%	194 total 97 HCC	Mean Age 68 Male 68%
Lam, E., Lam, C. et al. (2009) [46]	Asia	Not provided	SF-36	Child–Pugh A 68% B 8% C 3%	520 total 123 HCC	Mean Age 57 Male 85%
Li, L., Mo, F. et al. (2019) [47]	Asia	Not provided	EORTC QLQ-C30	Child–Pugh A 68% B 27% C 5%	472	Age ≤ 65: 69% Male 89%
Meier, A., Yopp, A. et al. (2015) [48]	North America	Not provided	EORTC QLQ-C30	Not specified	130	Mean Age 57 Male 78%
Mikoshiba, N., Miyashita, M. et al. (2013) [49]	Asia	Not provided	EORTC QLQ-C30	Child-Push A 76% Remaining 24% not specified	127	Mean Age 69 Male 81%

Table 1 (continued)

References	Location	QOL definition	QOL measure	Disease stage	Sample size	Sample demographics
Palmieri, V., Santovito, D. et al. (2015) [50]	Europe	Not provided	SF-36	Child–Pugh A 87% B 13%	66 total 24 HCC	Median Age 71 Male 75%
Phillips, R., Gandhi, M. et al. (2015) [33]	Asia	Provided	EORTC QLQ-C30	Not specified	167 HCC	Mean Age 56 Male 86%
Qiao, C., Zhai, X. et al. (2012) [51]	Asia	Not provided	EORTC QLQ-C30	Child–Pugh A 60% B 21% C 19%	140	Median Age 52 Male 95%
Ryu, E., Kim, K. et al. (2010) [52]	Asia	Not provided	FACT	Child–Pugh A 60% B 21% C 19%	180	Mean Age 55 Male 89%
Shiraki, M., Nishiguchi, S. et al. (2013) [53]	Asia	Not provided	SF-8	Child–Pugh A 55% B 23% C 22%	114 total 62 HCC	Not separated for HCC
Steel, J., Eton, D. et al. (2006) [54]	North America	Not provided	FACT	Not specified	158	Mean Age 64 Male 75%
Steel, J., Chopra, K. et al. (2007) [55]	North America	Not provided	FACT	Child–Pugh A 51% B 26% C 1% Missing 22%	272 total 83 HCC	Mean Age 58 Male 77%
Steel, J., Hess, S. et al. (2005) [56]	North America	Not provided	FACT	Child–Pugh A 73% B 18% C 0% Missing 9%	44 total 21 HCC	Mean Age 65 Male 100%
Steel, J., Geller, D. & Carr, B. (2005) [57]	North America	Provided	FACT	Not specified	82 triads (patient, caregiver, oncologist)	Mean Age 59 Male 78%
Sternby Eilard, M., Hagström, H. et al. (2017) [58]	Europe	Not provided	EORTC QLQ-C30	Child–Pugh A 70% B 27% C 3%	185	Mean Age 67 Male 77%
Sun, V., Ferrell, B. et al. (2008) [59]	North America	Not provided	FACT FACIT-spirituality	Not specified	55 total 22 HCC	Age not provided Male 72%
Ueno, S., Tanabe, G. et al. (2002) [60]	Asia	Not provided	Non-validated measure	Child–Pugh A 94% B 6%	96	Age ≤ 65: 68% Male 81%
Wong, W. & Fielding, R. (2008) [61]	Asia	Not provided	FACT	Not specified	578 total 253 HCC	Mean Age 57 Male 82%
Yeo, W., Mo, F. et al. (2006) [62]	Asia	Not provided	EORTC QLQ-C30	Child–Pugh A 69% B 27% C 4%	233	Median Age 57 Male 91%
Zheng, W., Wu, J. et al. (2013) [63]	Asia	Not provided	FACT	Not specified	62	Mean Age 49 Male 84%

(SF-8), was used in 5 (17%) studies. The remaining studies ($n = 2$) did not use a standard QOL measurement tool. For example, Gill et al. (2018) simply asked participants to describe their QOL as either "excellent", "good", or "poor", while Ueno et al. (2002) used a 14-item questionnaire asking participants to rate their physical, mental, and social health and symptoms as "good", "fair", or "poor" or "never", "sometimes" or "often" based on the question.

Table 2 Included domains of quality of life

References	QOL Measure	Physical Domains	Psychological Domain	Social Domain	Spiritual Domain	Liver Specific Measure
Bianchi, G., Loguercio, C. et al. (2003)	SF-36	Yes	Yes	Yes	No	None
Bonnetain, F., Paoletti, X. et al. (2008)	EORTC QLQ-C30	Yes	Yes	Yes	No	None
Chie, W.C., Blazeby, J.M. et al. (2017)	EORTC QLQ-C30	Yes	Yes	Yes	No	EORTC HCC 18
Diouf, M., Bonnetain, F. et al. (2015)	EORTC QLQ-C30	Yes	Yes	Yes	No	None
Fan, S., Eiser, C. et al. (2013)	EORTC QLQ-C30	Yes	Yes	Yes	No	EORTC HCC 18
Gill, J., Baiceanu, A. et al. (2018)	Patient reported: 'excellent', 'good', or 'poor' to describe their QOL	Yes	Yes	No	No	None
Gmür, A., Kolly, P. et al. (2018)	FACT	Yes	Yes	Yes	No	FACT-Hep
Hsu, W., Tsai, A. et al. (2012)	EORTC QLQ-C30	Yes	Yes	Yes	No	None
Jie, B., Qiu, Y. et al. (2015)	EORTC QLQ-C30	Yes	Yes	Yes	No	None
Kim, G., Kim, H. et al. (2019)	EORTC QLQ-C30 FACT	Yes	Yes	Yes	No	EORTC HCC 18
Kondo, Y., Yoshida, H. et al. (2007)	SF-36	Yes	Yes	Yes	No	None
Lam, E., Lam, C. et al. (2009)	SF-36	Yes	Yes	Yes	No	Chronic Liver Disease Questionnaire
Li, L., Mo, F. et al. (2019)	EORTC QLQ-C30	Yes	Yes	Yes	No	EORTC HCC 18
Meier, A., Yopp, A. et al. (2015)	EORTC QLQ-C30	Yes	Yes	Yes	No	EORTC HCC 18
Mikoshiba, N., Miyashita, M. et al. (2013)	EORTC QLQ-C30	Yes	Yes	Yes	No	EORTC HCC 18
Palmieri, V., Santovito, D. et al. (2015)	SF-36	Yes	Yes	Yes	No	None
Phillips, R., Gandhi, M. et al. (2015)	EORTC QLQ-C30	Yes	Yes	Yes	No	None
Qiao, C., Zhai, X. et al. (2012)	EORTC QLQ-C30	Yes	Yes	Yes	No	FACT-Hep
Ryu, E., Kim, K. et al. (2010)	FACT	Yes	Yes	Yes	No	FACT-Hep
Shiraki, M., Nishiguchi, S. et al. (2013)	SF-8	Yes	Yes	Yes	No	None
Steel, J., Eton, D. et al. (2006)	FACT	Yes	Yes	Yes	No	FACT-Hep
Steel, J., Chopra, K. et al. (2007)	FACT	Yes	Yes	Yes	No	FACT-Hep
Steel, J., Hess, S. et al. (2005)	FACT	Yes	Yes	Yes	No	FACT-Hep
Steel, J., Geller, D. & Carr, B. (2005)	FACT	Yes	Yes	Yes	No	FACT-Hep
Sternby Eilard, M., Hagström, H. et al. (2017)	EORTC QLQ-C30	Yes	Yes	Yes	No	EORTC HCC 18
Sun, V., Ferrell, B. et al. (2008)	FACT FACIT-Spirituality	Yes	Yes	Yes	Yes	FACT-Hep
Ueno, S., Tanabe, G. et al. (2002)	Non-validated measure	Yes	Yes	Yes	No	None
Wong, W. & Fielding, R. (2008)	FACT	Yes	Yes	Yes	No	None
Yeo, W., Mo, F. et al. (2006)	EORTC QLQ-C30	Yes	Yes	Yes	No	None
Zheng, W., Wu, J. et al. (2013)	FACT	Yes	Yes	Yes	No	FACT-Hep

QOL domains

The model of QOL for this review included four sub-domains of well-being: physical, psychological, social, and spiritual. A breakdown of the QOL measurement tools used in the articles for this review is presented in Table 2. All 30 (100%) of the studies addressed *physical* and *psychological* well-being and 29 (97%) included some measurement of the *social* domain of QOL; however, only one (3%) study specifically addressed the *spiritual* domain of QOL in any way.

Disease-specific measurement

Adults with HCC have a very specific set of symptoms resulting in a high symptom burden. One way to assess these symptoms is through a disease-specific QOL subscale; such a subscale was included in 17 (57%) studies. For example, both the EORTC and the FACT have disease-specific subscales appropriate for the HCC population; however, there is no relevant disease-specific subscale for the SF-36. The EORTC disease-specific subscale (EORTC HCC 18) was used in seven (23%) of studies and the FACT hepatobiliary (FACT-Hep) disease-specific subscale was used in nine (30%) studies. Kondo et al. (2007), who used the SF-36, added a chronic liver disease questionnaire to address the specific needs of the HCC population.

Discussion

The primary aims of this review were to identify how QOL is being defined and measured in the HCC literature, using Ferrell's model of QOL and sub-domains as a guiding lens. There were four insights and/or gaps identified.

First, only 10% of the studies included a definition for QOL. All three of these studies provided a definition of QOL that included aspects of physical, psychological, and social health; however, none of the definitions provided specifically addressed the spiritual well-being aspect of QOL. Without a clear or shared comprehensive definition of QOL, it is difficult to make inferences within/across research studies. The definition closely aligned with Ferrell's was the WHO definition (Steel et al. 2005), which states that QOL is much more than simply the absence of disease, but encompasses physical, mental, and social well-being [13]. However, The WHO definition of QOL does not specifically address the spiritual well-being as a fourth domain of QOL.

Second, there was the lack of attention to the *spiritual* domain of QOL in the HCC literature. Spiritual well-being was addressed in only one study. This absence may be because the spiritual domain has previously been housed or subsumed within the psychological domain of QOL; however, Ferrell asserts that it is its own separate domain [19]. According to Ferrell, the spiritual domain embodies more than religiosity and includes such topics as hope, inner strength, spirituality, uncertainty, transcendence, and meaning in illness [19]. In fact, a large study of adults with cancer found that spiritual well-being was a significant protective factor against psychological distress at the end of life [25]. A study of Italian cancer survivors found that faith, meaning, and peace became more important the closer survivors were to death [26]. Clearly, addressing the spiritual domain of QOL should be seen as essential, especially in life-limiting cancers, such as HCC [27]. Of note, the most commonly used QOL measurement tools (e.g., EORTC QLQ-C30, FACT, SF-36(8)) focus on the physical, psychological, and social domains, but do not specifically contain the spiritual domain. Both the EORTC and the FACT do have separate, spirituality-specific measurement tools, but these tools are only provided as a secondary questionnaire for study participants to complete. By separating this domain and only assessing it with the addition of another measurement tool, not only marginalizes this overlooked domain, but also increases the participant burden during research.

Third, there is a disproportionate geographic representation in HCC QOL research. HCC is endemic and a leading cause of cancer-related deaths in Eastern Asia (e. g., Mongolia, China), South-Eastern Asia, Northern and Western Africa, and Micronesia [3]. In fact, Asia is responsible for approximately 75% of the worldwide incidence of HCC, yet only 60% of the articles included in this review included participants from Asia. Worldwide, Mongolia has the highest incidence and mortality from HCC, which accounts for almost half of all cancer deaths in that country, yet no studies included participants from Mongolia [28]. Another large geographic location that was not represented was Africa, which was not represented in any of the study populations of this review yet HCC is prevalent throughout Africa, specifically in Northern and Western Africa where HCC is endemic [29]. In order to have a complete understanding of QOL in HCC, research in QOL in these areas of high HCC prevalence should be completed. In addition, the specific impact of HCC on QOL for these populations may be uniquely different.

Fourth and last, there was a lack of focus on QOL in the end-stage (Class C) HCC literature. Adults with HCC who are diagnosed and treated early (Classes A & B) have a greater rate of long-term survival and curative treatment available than those diagnosed late in class C. However, the majority of adults with HCC continue to be diagnosed in the late stages of disease, when long-term, curative treatment is no longer an option, and 1-year survival is less than 50% [30]. As such, end-stage HCC patients could possible present a uniquely different perspective on QOL than their early-stage counterparts. Only 68% of studies included in this review included Class C HCC participants. Further,

while 68% of the studies included Class C, 92% had less than 25% Class C participants. This under-representation is important in that the impact of HCC on QOL in end-stage disease may be at its highest, not only due to the increasing symptom burden experienced as patients approach death, but also because of an increase in self-awareness for anyone in the midst of facing death.

The most commonly used QOL tools were the EORTC QLQ-C30and the FACT. The EORTC QLQ-C30 includes five sub-domains: physical, emotional, cognitive, social, and role health [31]. The FACT includes three sub-domains: functional, emotional, and social health, plus a single item relating to the relationship with oncologist [32]. The EORTC QLQ-C30 addresses eight specific symptoms related to cancer and its treatment: fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea [33]. Though these eight symptoms are not pulled out as part of scoring, as with the EORTC QLQ-C30, the FACT also includes items regarding symptoms, such as fatigue, nausea, and pain within the functional health sub-domain [32]. As adults with HCC are known to have a high symptom burden, the EORTC QLQ-C30 may be a more appropriate measurement tool based on its ability to address more of symptoms experienced by adults with HCC.

While the majority of patients diagnosed with HCC are diagnosed in the advanced stage, the majority of QOL research is completed with those in the early stage of HCC. This skew in participation may reflect the high symptom burden and overt inability of patients in end-stage HCC to participate. However, it is worth noting as the experience in these individuals, again, may be distinctly different. Curative treatments, such as liver resection, liver transplant and ablation, are available for adults with HCC in the earlier stages, [7, 34]. When curative treatments are no longer an option, palliative treatment options may be offered, including: transarterial chemoembolization, chemotherapy (Sorafenib), and radiotherapy [34]. Side effects of these palliative treatments can be very similar to the symptoms of HCC, adding to, rather than decreasing symptom burden [34]. Though the EORTC QLQ-C30 and the FACT address the symptoms of fatigue, nausea, vomiting, pain, dyspnea, appetite changes, and diarrhea, these tools do not address other common symptoms as hypoglycemia, fever, cholangitis, peritonitis, and encephalopathy. In order to capture the overall experience of QOL in HCC, additional measures from the EORTC and FACT are needed or these tools need to be revisited as we learn more about HCC across its disease trajectory. Both the EORTC and the FACT have additional subscales available to address these specific needs of the HCC population; however, these measures may not always be appropriate, due to survey burden for study participants.

There are several limitations that need to be highlighted. First, we excluded articles that were not available in English. This exclusion may have underrepresented studies HCC-endemic areas, such as Asia, Though HCC is increasing in English-speaking countries, it is possible that research examining QOL has been done in these areas that is not available in English. Second, this review excluded research using qualitative methods due to our focus on investigating the definition of QOL being used and how QOL is measured in the HCC literature. The inclusion of qualitative studies may not only provide a deeper view of what QOL means to the patient with HCC, but also provide additional insights into how existing tools could capture QOL across domains and disease stages. Finally, this review shows clear gaps in the literature for the HCC population, which may not be generalizable to other types of cancers that are not increasing in incidence and mortality. Similar studies should be conducted in other life-limiting cancers, such as pancreatic cancer, to explore similarities and differences.

Conclusion

As the incidence and mortality of HCC continues to increase worldwide, the need to examine QOL in adults with HCC is increasingly important. This systematic review was completed to begin to investigate the current state of knowledge around QOL and HCC, with a focus on how QOL is currently defined and measured in the HCC literature. We also examined the inclusion of four QOL sub-domains using the model put forth by Ferrell et al. (1996). We found that in QOL studies in HCC, the physical, psychological, and social domains are well represented, but there was a lack of research into the spiritual domain of QOL. Of particular note, we found a lack of a clear definition of QOL in the overwhelming majority of the studies. This lack of definition may be due to the complex nature of the concept of QOL or an assumption that everyone knows what QOL means. Yet, even when definitions of QOL are included, there was a lack of specific attention to spirituality. This oversight clearly needs attention as research increasingly defines spirituality as a prognostic predictor of QOL. Finally, there is a need to explore QOL across the HCC experience, especially in end-stage disease and differences between/among genders, including those who self-identify as gender minorities, such as the LGBTQ populations. Each of these limitations provide an avenue for future research.

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