JGH Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.16107

REVIEW ARTICLE

Barriers to palliative care in hepatocellular carcinoma: A review of the literature

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Key words
Barriers, Hepatocellular carcinoma, Palliative care.

Accepted for publication 11 January 2023.

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Declaration of conflict of interest: No competing financial interests or other conflicts of interest exist.
Ethical approval: Data sourced in writing this review is available within the article. All figures are original and were created with BioRender.com with a granted publishing license.

Abstract

Hepatocellular carcinoma (HCC) is a deadly and burdensome form of liver cancer with an increasing global prevalence. Its course is unpredictable as it frequently occurs in the context of underlying end-stage liver disease, and the associated symptoms and adverse effects of treatment cause severe suffering for patients. Palliative care (PC) is a medical specialty that addresses the physical, emotional, and spiritual needs of patients and their carers in the context of life-limiting illness. In other cancers, a growing body of evidence has demonstrated that the early introduction of PC at diagnosis improves patient and carer outcomes. Despite this, the integration of palliative care at the diagnosis of HCC remains suboptimal, as patients usually receive PC only at the very terminal phase of their disease, even when diagnosed early. Significant barriers to the uptake of palliative care in the treatment algorithm of hepatocellular carcinoma fall under four main themes: data limitations, disease, clinician, and patient factors. Barriers relating to data limitations mainly encapsulated the risk of bias inherent in published work in the field of PC. Clinician-reported barriers related to negative attitudes towards PC and a lack of time for PC discussions. Barriers related to the disease align with prognostic uncertainty due to the unpredictable course of HCC. Significantly, there exists a paucity of evidence exploring patient-perceived barriers to timely PC implementation in HCC. Given that patients are often the underrepresented stakeholder in the delivery of PC, future research should explore the patient perspective in adequately designed qualitative studies as the first step.

Introduction

Palliative care (PC) has been integrated into the treatment algorithm of many terminal diseases in recent years,[1] with evidence suggesting early palliative care introduction at diagnosis improves survival, patient quality of life (QoL) and carer preparedness for the caregiving role.[2–4] Despite this, the early integration of PC at diagnosis (henceforth referred to as early PC) alongside the medical treatment of hepatocellular carcinoma (HCC) remains suboptimal, as patients with HCC usually receive PC only at the very terminal phase of their disease, even if diagnosed early[5] (Fig. 1).

Terminal HCC is defined by the Barcelona Clinic Liver Cancer (BCLC) staging system as BCLC-stage D, characterized by metastatic spread, a non-transplantable liver, poor hepatic function, and a poor patient performance status.[6] Therefore, this population could potentially benefit from an early PC consultation, mitigating the significant burden of disease associated with late-stage HCC. This review aimed to explore the literature relating to barriers to early PC implementation for people with HCC, while demonstrating the cogent need to accurately explicate these factors in order to maximize early PC uptake in this population.

Hepatocellular carcinoma

HCC is the most common primary malignancy of the liver and ranks second in global cancer- related mortality, despite ranking seventh in prevalence.[7] HCC eclipses all other cancers with respect to degree-of-fatality: It has a mortality-to-incidence ratio of 0.89, compared with pancreatic with 0.83, lung with 0.72, and colorectal cancer with 0.27.[6] This high mortality is attributable to various causes. For instance, while patients with HCC are likely to die from primary liver cancer, a substantial proportion will die from related causes, including non-malignant liver disease and other non-malignant illnesses, cancer from other sites, and suicide.[8]

In Australia, the incidence of HCC has increased markedly from 1.38/100 000 in 1982 to 4.96/100 000 in 2014, with likely driving factors comprising an aging population, increased migration from

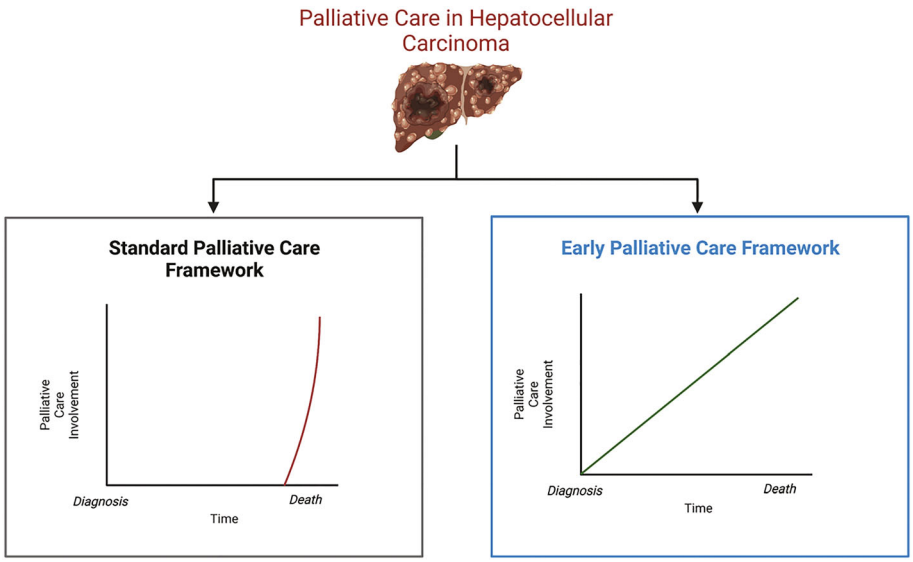

FIGURE 1 Current hepatocellular carcinoma (HCC) treatment algorithms utilize the standard palliative care framework, while evidence recommends the early palliative care framework. Created with BioRender.com.

hepatitis B virus (HBV) endemic countries and the emerging prevalence of metabolic syndrome, hepatitis C virus (HCV), type 2 diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD).[6,9,10]

The variable course of HCC. HCC is a complex disease, underscored by an unpredictable course.[11] This is largely attributable to the fact that it frequently occurs in the context of underlying end-stage liver disease (ESLD), with 85%–90% of cases transpiring in this manner.[7] ESLD is the final phase in the course of any chronic liver disease.[12] Its causes include viral hepatitis due to chronic HCV or HBV, alcoholic liver disease, and NAFLD on a background of obesity and metabolic syndrome. Chronic liver disease eventuates in the development of liver cirrhosis, the key precursor for HCC.[13,14]

Unfortunately, the reality of a binate HCC/ESLD presentation renders the health trajectory of an individual HCC patient dependent not only on tumor-related factors, including the size, biologic behavior, and spread of the cancer, but also on the degree of hepatic functional failure in ESLD.[11] This latter point is complicated by the ability of the liver to recover function, rendering ESLD a disease with variable course.[15] Accordingly, the health trajectory of patients presenting with both is unpredictable, characterized by episodic and acute exacerbations, as well as frequent hospitalizations and stabilizations.[16] Therefore, appropriate early PC is essential to ensure symptoms and sequelae of disease are controlled before they assume a turbulent course.

Symptom burden. Because of the underlying ESLD, patients with HCC suffer from symptoms of both liver failure and cancer.[17] The former is characterized by the development of jaundice, ascites, variceal hemorrhage and hepatic encephalopathy, each with its own unique management challenges and prognostic implications.[16] When combined with HCC and its long and protracted treatment journey, patients with this typical dual presentation are subject to severe physical and psychological burden.[18,19] A recent and extensive meta-analysis by Tan et al. found that in 64 247 patients with HCC, one in four suffered from depression, while one in five suffered from anxiety.[20] In line with this, individuals with HCC suffer the third highest reported levels of psychological stress among people with the 14 leading cancers.[21] Despite this, the severe physical and psychosocial burden of liver disease is not addressed for patients with liver disease until late in the treatment course, near the terminal stage.[22]

Palliative care and its role in HCC

Palliative care is a relatively neoteric medical specialty. Initially established to provide pain relief to patients at the end-of-life,[23] the definition of PC has evolved significantly over time. In addition to pain relief, still a core tenet of PC, best practice now involves addressing and holistically managing the physical, emotional, and spiritual needs of patients and their families or carers in the context of life limiting illness.[24–26] In other advanced cancers, published guidelines have suggested the implementation of the early PC framework (Figure 1), whereby patients receive dedicated PC services concurrent with active treatment early in the disease course, at or near diagnosis.[5] In HCC, implementing the early PC framework congruently with disease-modifying therapy would best be achieved through the PC multidisciplinary team, optimally consisting of specialist PC physicians and nurses, hepatologists, and allied healthcare workers (including a social worker, physiotherapist, speech pathologist, occupational therapist, and dietitian), with access to pastoral care and bereavement counsellors.[6] Multidisciplinary care has been shown to improve the overall survival of patients with HCC by reducing time to treatment after diagnosis, increasing adherence to clinical guidelines, and improving staging and diagnostic accuracy.[7] A retrospective cohort study by Yopp et al. has evidenced this, with patients experiencing multidisciplinary care encountering fewer symptoms at presentation (64 *vs* 78%, $P = 0.01$), shorter median time to

treatment after diagnosis (2.3 months *vs* 5.3 months, $P = 0.002$), and greater median survival (13.2 months *vs* 4.8 months, $P = 0.005$).[27]

Evidence supporting early PC integration in other malignant diseases. In a recent trial measuring QoL as the primary outcome, Vanbutsele et al.[28] randomly assigned 133 patients with advanced cancer to receive either standard oncological care or an early PC intervention delivered by a team of specialist PC physicians and nurses within 12 weeks of diagnosis. QoL was assessed by the McGill Questionnaire,[29] which observed a statistically significant trend favoring the PC-arm (7.05 *vs* 5.94; $P = 0.0006$).[28] These findings were galvanized by a large cluster randomized controlled trial (RCT), comparing early specialist PC (introduced to patients with a prognosis of 6–24 months) to routine oncological care in 461 patients with metastatic tumors.[30] In this trial, patients in the early PC-arm experienced overall decreased symptom burden and increased QoL, reaching statistical significance at 4 months, whereas the control group declined in these areas (+2.46 *vs* −3.95; $P = 0.006$).[30] Evidence has also shown the potential role of early PC integration in improving survival. Temel et al.[31] enrolled 151 patients randomized to receive standard oncological care either exclusively or in conjunction with an early specialist PC intervention, who were introduced within 8 weeks of an advanced lung cancer diagnosis. Of note, patients in the early PC-arm experienced less aggressive care at the end of life and increased length of life (median, 11.6 months *vs* 8.9 months; $P = 0.02$).[31]

In contrast, one trial reported limited benefit of early PC integration, introduced within 60 days of diagnosis of advanced-stage cancer, compared with delayed PC initiated 3 months later.[32] The results showed no difference in QoL, mood, and symptom burden between the groups. However, the results were arguably invalidated by exposure of the controls to the intervention, with half of the delayed-care group receiving a PC consultation prior to implementation of the intervention, thereby diluting the interventional impact.[32] Although there is conflicting evidence, the literature demonstrates that early PC integration improves outcomes in both patients and caregivers. Several prospective cohort and retrospective studies have also provided lower level evidence of this (level II and level III quality evidence,[33] respectively).[34–36]

From the perspective of cost–benefit and resources, several RCTs have demonstrated that early PC integration reduces readmission rates, hospital resource usage and economic costs in various life-limiting illnesses. Gade et al. randomized 517 patients with life-limiting conditions to receive either usual hospital care or interdisciplinary early PC services. Patients in the early PC intervention group had fewer intensive care admissions ($P < 0.04$) and had net cost savings of $4,855 USD per patient compared with the control group ($P < 0.001$).[37] In another US-based RCT, 298 terminally-ill participants were randomized to usual or in-home palliative care services. Patients randomized to in-home PC were more likely to die at home than those receiving standard care ($P < 0.001$), thereby avoiding readmission. Moreover, participants in the PC intervention group were less likely to visit the emergency department compared with those receiving standard care ($P < 0.001$). These combined factors resulted in significantly lower care costs for intervention patients ($P = 0.03$).[38] While no RCTs have been performed in the HCC cohort examining cost–benefit analysis for early PC, several studies have established an association between PC utilization in HCC and reduced healthcare costs. For example, in a Canadian-based population study, Thein et al. found that terminal HCC care was the most expensive phase of care, especially when delivered in the acute inpatient setting, where over half of terminal phase costs stemmed. At the same time, only 4.1% of terminal phase costs were attributed to home care.[39] When combined with the finding that patients who receive early PC have lower rates of hospitalization and ICU admissions,[37,38] we can infer that early PC involvement reduces the costs associated with an acute inpatient stay. This is important because HCC imposes a severe economic burden on patients and the health system.[6] Australian cohort estimates place the per-patient healthcare cost at approximately $31 775 AUD per annum, totaling $139.5 million AUD in total health system expenditure.[40] Therefore, early PC referral is crucial in mitigating these high costs by preventing hospital admissions and inpatient deaths and shifting care towards the home setting, reducing costly inpatient expenditure for HCC.

Barriers to palliative care integration in HCC

A review of the current evidence suggests that barriers to PC integration fall within four themes: data limitations, disease factors, clinician factors, and patient factors (Fig. 2).

Data limitations. There is currently no evidence to guide the optimal time to introduce PC in the trajectory of HCC. RCTs demonstrate several potential barriers to early PC integration in terminal diseases. First, significant uncertainty exists over what is considered "early" (Table 1).[41] From the trials cited above, "early" PC integration has been defined in relation to time of death[30] or time from diagnosis.[28,31,32] A literature review found authors opting to define early PC integration using specific disease stages[42] or disease symptom burden evaluated using assessment tools.[43] This suggests that a standardized definition of "early integration" would be a key factor in increasing early PC uptake.

Second, important methodological flaws permeate the PC literature. All recently published systematic reviews evaluating the association between early PC integration and patient and caregiver outcomes reported that results in the majority of the reviewed RCTs (including those analyzed above) should be interpreted with caution due to the significant risk of bias inherent in their respective methodologies.[45–51] This bias arises from marked heterogeneity between trials with respect to the interventions, endpoints, and population demographics (Tables 2 and 3).

These findings are indicative of an incongruence between PC research and the principles of evidence-based medicine—for a trial to be valid, a homogenous population should be selected utilizing a single well-defined intervention, and outcomes should be subsequently analyzed with objective and clinically relevant endpoints.[52] PC is inherently challenging with these paradigms because of the following:

1 The PC population is considerably heterogenous, encapsulating a vast array of backgrounds and diseases.[53]

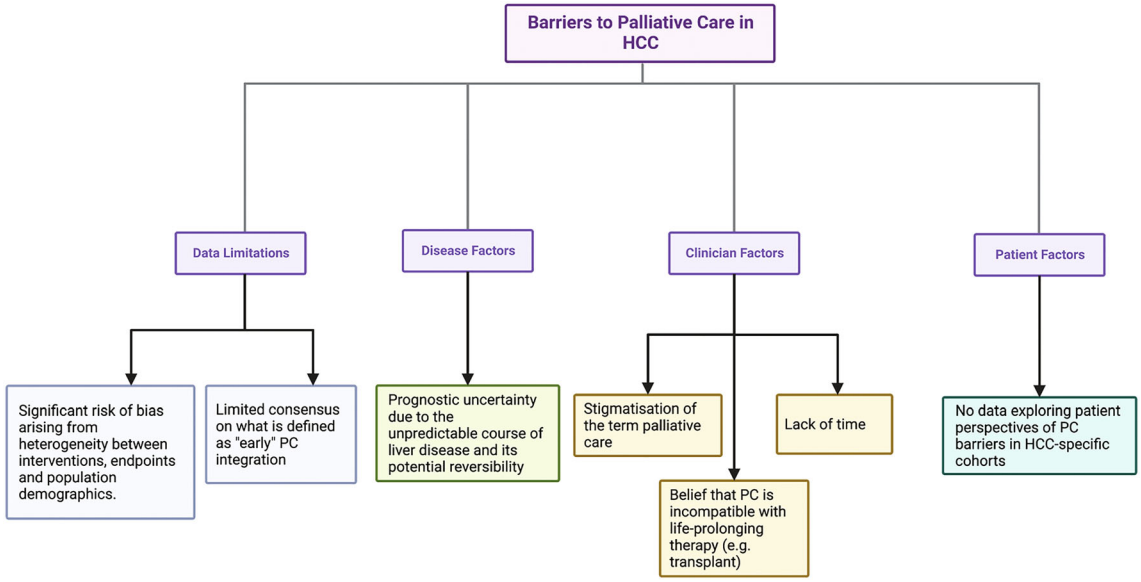

FIGURE 2 Our identified barriers to early implementation of palliative care in HCC. Created with BioRender.com.

Table 1 Various definitions of "early PC" identified in the literature

Category used to define *early PC* identified in the literature	Variations of definition across the literature
Disease stage	HCC stage BCLC0–C[44]
	COPD GOLD stage III or IV[42]
Time after diagnosis	Within 8–12 weeks of diagnosis[3]
	Within 8 weeks of diagnosis[31]
	Within 30–60 days of diagnosis[32]
Prognosis	Prognosis of 1 year[28]
	Prognosis of 6–24 months[30,32]
Time before death	>3 months before death[34]
Symptom burden	Evaluated using symptom assessment tools (e.g. ESAS, QUAL-E)[43]
	Evaluated using ECOG[30]
Other	If eligible for liver transplantation evaluation[26]
	Diagnosis of incurability[43]

BCLC, Barcelona Clinic Liver Cancer staging system; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group performance status scale; ESAS, Edmonton Symptom Assessment System; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCC, hepatocellular carcinoma; PC, palliative care; QUAL-E, Quality of Life at the End of Life Questionnaire.

Table 2 Various endpoints assessed in RCTs comparing early PC to delayed PC or standard oncological care

Endpoints assessed in RCTs	Method of assessment of endpoint
Quality of life	FACIT[3,30,32]
	EORTC QLQ-C30[28]
	QUAL-E[30]
	MQOL[28]
	FACT[31,44]
Symptom intensity	ESAS[3,30,44]
	QUAL-E[32]
Mood	ESDS[3]
	Modified ESAS[26]
	CES-D[26,32]
	HADS[31]
Satisfaction with care	FAMCARE-P16[30]
Issues with medical professional interactions	CARES-MIS[30]
Other	Survival[32]

Note: the great variation that exists across the PC literature in assessing each identified endpoint.

CARES-MIS, Cancer Rehabilitation Evaluation System Medical Interaction Subscale; CES-D, Centre for Epidemiologic Studies Depression Scale; EORTC, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ESAS, Edmonton Symptom Assessment System; ESDS, Emotional Self-Disclosure Scale; FACIT, Functional Assessment of Chronic Illness Therapy scale; FACT, Functional Assessment of Cancer Therapy; FAMCARE-P16, Family Satisfaction with Advanced Cancer Care 16-item scale; HADS, Hospital Anxiety and Depression Scale; MQOL, McGill Quality of Life Questionnaire; QUAL-E, Quality of Life at the End of Life Questionnaire; RCT, randomized controlled trial.

2 PC often involves implementing multiple interventions at once, as it addresses the holistic needs of a patient. Thus, there is substantial difficulty in controlling for the effects of interventions.[46,52]

3 Traditional RCT endpoints, such as death and disability, are inappropriate for the palliative population as the primary

goal is to improve QoL.[54] Alternative endpoints frequently utilized in PC lie on a spectrum of reliability—for example, the spiritual effects of PC are difficult to quantify, unlike outcomes such as pain.[55,56] However, the use of validated tools may mitigate this challenge and introduce more consistency and objectivity in assessment.[57]

As a result of the high degree of variability of primary data, several clinical guidelines issued by major hepatology societies around the world fail to recommend early PC integration at diagnosis of HCC.[58–60] For instance, clinical practice guidelines stop short of recommending palliative care, referring only to "best supportive care", and even then, only for BCLC-D HCC even if diagnosis occurs in the early stages.[58,61] This is despite numerous primary studies demonstrating the benefit of early PC integration across all phases of management.[2,3,6,16,24,26,30,31,44] In this regard, many of the services provided by PC, including symptom management, care coordination, psychosocial support, and decisional support, extend across all stages of HCC including the early stages, when curative treatments are still available[6] (Table 4). However, despite the reluctance of hepatological societies to recommend early PC, recently published clinical guidelines by the Korean Liver Cancer Association acknowledged the benefits of early and active PC on quality of life and symptom control in HCC.[62] This may indicate a global shift towards recognizing the role that PC can foster in managing HCC.

Table 3 Heterogeneity of population composition in palliative care RCTs comparing early PC to delayed PC or standard oncological care

Category	Population composition
Etiology	Advanced cancer, including gastrointestinal, lung, genitourinary, breast, and gynaecological[3,28,30,32]
	End-stage liver disease[26]
	Non-small cell lung cancer[31]
	Hepatocellular carcinoma[44]
Age (years)	51–60[26,28]
	>60[3,30–32]
Sex	Predominantly male[3,26,28,44]
	Predominantly female[30–32]
Ethnicity	Caucasian[3,30–32]
	Not disclosed[26,44]

Note: It is difficult to pool data from these randomized controlled trial (RCTs) to form clinically meaningful results partly due to the diversity of the palliative care (PC) population, illustrated in the table.

Disease factors. As aforementioned, the unpredictable course of HCC and ESLD lends itself to prognostic uncertainty.[16] In addition to the potential reversibility of liver cirrhosis, the course of ESLD can fluctuate between phases of compensation and decompensation, thereby rendering it difficult to estimate the point of irreversible hepatic failure.[63] A focus group study with 22 liver clinicians found that the difficulty in estimating the point of irreversible liver decline provides doctors with the hope that trying different active and often invasive treatments might promote recovery, resulting in a reluctance to hold PC and advance care planning discussions with patients.[64] Along this line, active and invasive treatment can cause significant harm in patients unsuitable for further treatment. For instance, transarterial chemoembolization, commonly utilized in intermediate disease, can induce hepatic deterioration if used incorrectly in unsuitable recipients.[61]

However, PC intervention in liver disease should be unrelated to the timing of irreversible hepatic failure and needs to be introduced long before this point, parallel to curative therapy.[6] While

Table 4 Potential role of PC across all stages of HCC

HCC stage	HCC therapy options	Typical symptoms	Role of palliative care in each stage
Early (BCLC stage 0-A) Single nodule <2 cm, PST 0, Child–Pugh A	• Liver resection • Liver transplant • Ablation (RF/PEI)	• Adverse effects of treatment including pain, infection, fever	• Symptom control • Disease education • Advance care planning and goals of care discussion
Intermediate (BCLC stage B) Multinodular, PS 0, Child–Pugh A/B	• TACE	• Adverse effects of treatment including nausea, vomiting, pain, fever, fatigue • Local symptoms of primary tumor • Extrahepatic symptoms	• Address the physical, psychosocial, and spiritual needs of patients through symptom control, counseling, and pastoral care services respectively • Assistance with decision making and navigation through treatment pathways
Advanced (BCLC stage C) Portal invasion, N1, M1, PS 1–2, Child–Pugh B	• Systemic chemotherapy (e.g., Sorafenib)	• Adverse effects of treatment (skin reaction, diarrhea, anorexia, fatigue) • Local symptoms of primary tumor • Extrahepatic symptoms	
Late-stage/terminal (BCLC Stage D) PST > 2, Child–Pugh C	• Best supportive care (appropriate palliative care)	• Local symptoms of primary tumor • Extrahepatic symptoms (fatigue, anorexia) • Liver failure (jaundice, ascites, and encephalopathy) • Metastatic disease (symptoms related to system of metastases, e.g., dyspnoea, pain)	• Symptom control • End-of-life care • Provision of resources (e.g., inpatient palliative care unit and community palliative care services and equipment) • Family support and bereavement counseling

Note: Palliative care (PC) has a distinct and valuable place across all stages of hepatocellular carcinoma (HCC).

ostensibly improving patient and carer outcomes, early introduction would also bypass the confusion regarding disease course, as it would make the difficult task of estimating irreversible liver decline unnecessary. Moreover, PC has shifted towards a needs-based modality of care, rather than depending on the prognosis, aligning with the profile of the HCC patient population.[65] In this regard, introduction of PC is independent of the prognostic turbulence of ESLD and HCC and can be introduced either at diagnosis or on-demand in this population.

Clinician factors. Clinician barriers to PC implementation have been well explored in the literature. One major barrier identified is the stigma around the use of the term "palliative care" by practitioners.[66] Misperceptions that equate PC with end-of-life care may impact when and how often HCC patients are referred to PC in addition to their disease-directed therapy.[67] Several questionnaire-based cohort studies revealed a belief among some medical oncologists that PC is not compatible with cancer-directed treatment and instead should be reserved as an end-of-life management modality.[68–70]

Ufere et al.[71] conducted a large cross-sectional survey of 396 hepatologists and gastroenterologists, finding that these clinicians perceived significant barriers to PC implementation in patients with ESLD, including fear that the phrase 'palliative care' destroys patients' hope (82%), and belief that PC only begins when active therapy ends (81%).[71] It is likely that these perceived barriers source from a lack of education in PC principles.[72]

In line with this, we identified two overarching correctors of clinician misperceptions in the literature: clinician education of PC principles and renaming PC to "supportive care." Regarding the former, while the stigma endorsed by clinicians regarding PC have been discussed above, survey studies have also revealed that oncologists had mixed opinions about their training and competence in PC delivery. In line with this knowledge gap, several initiatives have been implemented in different global settings to develop PC education curriculums for healthcare professionals. For instance, the Palliative care Emphasis program on symptom management and Assessment for Continuous medical Education (PEACE) is a Japanese program with nine modules targeting pain management, psychosocial care and communication skills.[73] Over 37 000 clinicians have completed the program, and in a before–after comparison of 85 physicians, researchers noted statistically significant improvements in PC knowledge ($P < 0.0001$) and self-reported competency in PC delivery ($P < 0.0001$).[74]

Moreover, in addition to an education initiative, renaming PC has been identified as a supplemental enabler to PC uptake in life-limiting illnesses. Considering this, a PC unit in a US hospital changed its name to "supportive care," and in a before–after comparison, the number of referrals significantly increased by 41% ($P < 0.001$), and outpatients were referred earlier (median time from hospital registration to PC consultation; 9.2 months *vs* 13.2 months; $P < 0.001$).[75] Additionally, in another extensive survey of 182 haematologic and solid tumor oncologists, a significantly greater proportion of specialists reported that they would refer a patient with newly diagnosed cancer to "supportive care" rather than "palliative care" (81% *vs* 43%; $P < 0.001$). These clinicians also believed that PC was more likely to be a barrier for referral than supportive care (36% *vs* 3%; $P < 0.001$) and that PC was also synonymous with hospice and end-of-life care (53% *vs* 6%; $P < 0.001$).[72] Other studies have supported this notion,[70,76] and while no data have been conducted in an HCC-specific population exploring a possible name change, data in other cancers and chronic diseases suggest that renaming palliative care to supportive care could be a great enabler in improving PC uptake in traditionally underserved populations.

Finally, clinicians (as well as patients) find offering curative treatment such as a liver transplant and introducing PC simultaneously to patients awaiting curative therapies challenging,[66] assuming that PC focuses on the provision of end-of-life care while transplantation prolongs life.[67,68] However, ESLD patients who receive PC referrals concurrently with liver transplantation evaluation have improved symptom control, fewer depressive symptoms,[26] a decreased surgical intensive care unit stay, and increased discussions surrounding goals of care.[77]

Patient factors. There is a paucity of studies that explore the perceived barriers of HCC patients to timely PC integration at diagnosis. In fact, where there is discussion of patient attitudes, it is either reported from the physician viewpoint[71] or geared towards an aspect of PC unrelated to the barriers to early PC implementation.[78–80] This follows from a general reluctance in hepatology to discuss end-of-life matters with patients, as clinicians either lack confidence in raising the topic of PC or feel that PC is irrelevant in the field, due to their assumption that liver disease can be reversed.[81] The current review did not identify any trials exploring patient perspectives in HCC-specific cohorts. Therefore, for the purposes of the review, we broadened our search to include ESLD, as the issues faced by both population groups are similar. Five primary trials, including two cohort studies and three cross-sectional surveys, investigated patients with advanced liver disease.[63,82–85] Their perceived barriers to PC integration were identified.

The most prominent theme was a lack of patient and caregiver education surrounding PC principles. This resulted in uncertainty, compounding the profound emotional distress patients were already experiencing. One longitudinal study by Zimmerman et al. was able to demonstrate a temporal change in patient perspectives of PC following an educational intervention about PC principles.[85] After the intervention, patients reported a "more comfortable" attitude towards PC, and much of the uncertainty and fear about their disease had been alleviated. Donlan et al. found that when educated about PC in an interview setting, many participants expressed a preference for the early introduction of PC in ESLD management.[83] The remaining three studies were cross-sectional surveys and gave little insight into the temporal link between PC intervention and patient perspectives.[63,82,84]

However, in all studies, several limitations were identified. No study explored the perceptions of an HCC-specific population. Further, the majority of studies utilized small sample sizes ($n < 40$),[63,82–84] with only one study achieving a moderately large cohort ($n = 71$).[85] The small sample size underpowers these studies and precludes strong evidence to inform clinical practice. Further investigations with adequately sized and powered populations are necessitated to inform clinical practice.

Additional limitations were primarily related to lack of generalizability and external validity, and the findings obtained from the

study populations may therefore not reflect the general population. First, all studies were performed at a single centre with patients hailing predominantly from European, English-speaking backgrounds. The lack of ethnic/racial diversity in study participants limits the generalizability of the results, including in multi-cultural countries such as Australia where the HCC/ESLD population includes over 50% of patients born overseas.[86] Culture and religion play a significant role in the acceptance of PC and may be a significant barrier to its delivery in a multicultural, diverse HCC population.[87] Second, two of the five studies lacked diversity of sex, age, and liver disease etiology in their sampled cohorts.[84,85] Finally, two studies predominantly included participants with an identified carer. This is not reflective of the ESLD/HCC population, as many patients do not have a designated caregiver.[82,83] Therefore, future studies utilizing purposive sampling in HCC-specific cohorts are necessary to mitigate concerns with study generalizability.

Summary and potential for future research

In summary, this review illustrates the need to draw attention to the important issue of poor PC integration in the HCC treatment algorithm. We highlight the advantages of introducing an early PC initiative to the HCC cohort, identifying advantages such as improved QoL and survival, cost–benefit, and reduced hospitalization and admissions. However, in the peer-reviewed PC literature, there is a lack of research regarding the integration of PC in HCC. This is due to a considerable diversity surrounding the definition of "early" PC integration, methodological limitations of studies including issues of heterogeneity and bias, and most importantly, the lack of patient perspectives. A recent systematic review investigating this topic identified only eight trials exploring patient perspectives in individuals with liver disease, none of which explored the perspectives of patients with HCC. It concluded that there was a paucity of information in a subject so pertinent, given the prevalence and mortality of liver disease in high income countries.[81]

Therefore, this review can stimulate research in multiple areas relating to PC in liver disease and HCC, in order to alter current medical practices and antecedent ideas pertaining to the delayed introduction of PC. For instance, there are no studies exploring the perspectives of patients living with HCC. Identified trials also failed to account for the diverse demographic composition of the HCC population. Given that patients are the most important stakeholders in the delivery of PC, it is crucial that their perceived barriers to early PC integration in HCC are accurately delineated, especially for traditionally underrepresented groups such as migrant populations. These should be explored in adequately designed, qualitative studies, a necessary step forward to alter current medical practices.

Acknowledgment

Open access publishing facilitated by University of New South Wales, as part of the Wiley - University of New South Wales agreement via the Council of Australian University Librarians.

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