

# Developing Priorities for Palliative Care Research in Advanced Liver Disease: A Multidisciplinary Approach

Arpan A. Patel <sup>1,2</sup>, Christopher Woodrell,<sup>3,4</sup> Nneka N. Ufere,<sup>5</sup> Lissi Hansen <sup>6</sup>, Puneeta Tandon,<sup>7,8</sup> Manisha Verma,<sup>9</sup> Jennifer Lai,<sup>10</sup> Rachel Pinotti,<sup>11</sup> Mina Rakoski,<sup>12</sup> and on behalf of the Palliative Care Education, Advocacy, and Research in Liver Disease (PEARL) Workgroup and the AASLD Public Health / Healthcare Delivery Special Interest Group (SIG)

Individuals with advanced liver disease (AdvLD), such as decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), have significant palliative needs. However, little research is available to guide health care providers on how to improve key domains related to palliative care (PC). We sought to identify priority areas for future research in PC by performing a comprehensive literature review and conducting iterative expert panel discussions. We conducted a literature review using search terms related to AdvLD and key PC domains. Individual reviews of these domains were performed, followed by iterative discussions by a panel consisting of experts from multiple disciplines, including hepatology, specialty PC, and nursing. Based on these discussions, priority areas for research were identified. We identified critical gaps in the available research related to PC and AdvLD. We developed and shared five key priority questions incorporating domains related to PC. *Conclusion:* Future research endeavors focused on improving PC in AdvLD should consider addressing the five key priorities areas identified from literature reviews and expert panel discussions. (*Hepatology Communications* 2021;5:1469-1480).

Individuals with advanced liver disease (AdvLD), such as decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), suffer from significantly reduced quality of life as well as high short-term mortality.<sup>(1-5)</sup> Standard medical care for these patients has traditionally focused on prolonging survival, and greater attention has only more recently been paid toward improving patient-reported outcomes (PROs).<sup>(6-8)</sup> However, these goals do not fully incorporate palliative care (PC), which is becoming increasingly recognized as an important facet of treating patients with serious illnesses like AdvLDs.<sup>(9-11)</sup>

The World Health Organization has defined PC as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.”<sup>(12)</sup> The Center to Advance Palliative Care further states that PC can be delivered at any stage of a serious illness and for patients of any age.<sup>(13)</sup> PC can be provided by a specially trained team of doctors, nurses, and specialists who work together

*Abbreviations:* ACP, advance care planning; AdvLD, advanced liver disease; DC, decompensated cirrhosis; GOC, goals of care; HCC, hepatocellular carcinoma; ICU, intensive care unit; MBSR, mindfulness-based stress reduction; MELD-Na, Model for End-Stage Liver Disease–Sodium; PC, palliative care.

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with a patient's primary treating team to provide an extra layer of support (specialty PC). Many aspects of PC can be and are often provided by the treating team themselves (primary PC).<sup>(14)</sup> Important domains of PC include not only PROs, such as physical symptoms, but also quality of communication and patient and caregiver psychological outcomes.<sup>(15)</sup>

Integration of PC has improved the quality of life and reduced health care use in many seriously ill populations, which may explain the immense demand for specialty services as well as their growth in the United States over the past 2 decades.<sup>(16,17)</sup> Guidelines developed for specialists treating patients with advanced cancer, advanced heart failure, end-stage renal disease, pulmonary diseases, and many other serious illnesses all advocate for early PC involvement in the management of patients with these diseases.<sup>(18-21)</sup> Unfortunately, no such guidelines have been developed for patients with AdvLD, which may be due to the fact that growth of research in this field is a relatively recent phenomenon.<sup>(22)</sup> In order to promote the development and dissemination of high-impact research in PC for AdvLD, more guidance is needed.

The primary objective of this paper is to identify major priority areas for researching PC outcomes in patients with AdvLD. In order to do this, our primary goals are to 1) identify critical gaps in evidence through a comprehensive review of the literature to date; 2) identify research priorities that will advance the field; and 3) suggest appropriate methodologies for future work. We have presented this information

within the framework of a case-based scenario to help contextualize this literature within the trajectory of a patient with AdvLD.

## Materials and Methods

We assembled an expert panel comprised of individuals from the disciplines of hepatology (A.P., N.N.U., M.V., P.T., M.R.), specialty PC (C.W., L.H.), and nursing (L.H.). We used a modified version of a scoping review methodology.<sup>(23-25)</sup> The first step was to conduct a comprehensive review of current studies involving PC domains in patients with AdvLD. Eight domains of interest were selected for this review based on the National Consensus Project Clinical Practice Guidelines for Quality Palliative Care as well as other topics that were deemed relevant to practice (Fig. 1).<sup>(26)</sup> In consultation with R.P., a medical librarian with expertise in search strategy development, we designed and executed a comprehensive search strategy of the literature in PubMed. Separate search strategies were developed, using PC terms derived from the eight domains of interest. Each search used all relevant medical subject heading terms and keywords related to PC, liver disease, and the domain of interest (Supporting Fig. S1), including search terms harvested from a published systematic review supporting the National Consensus Project Clinical Practice Guidelines for Quality Palliative Care.<sup>(16)</sup>

### ARTICLE INFORMATION:

From the <sup>1</sup>Vatche and Tamar Manoukian Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA; <sup>2</sup>Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, USA; <sup>3</sup>Brookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; <sup>4</sup>James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA; <sup>5</sup>Gastrointestinal Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; <sup>6</sup>School of Nursing, Oregon Health Sciences University, Portland, OR, USA; <sup>7</sup>Department of Medicine, Cirrhosis Care Clinic; <sup>8</sup>Liver Transplant Unit, University of Alberta, Edmonton, AL, Canada; <sup>9</sup>Department of Digestive Diseases and Transplantation, Einstein Healthcare Network, Philadelphia, PA, USA; <sup>10</sup>Division of Gastroenterology and Hepatology, Department of Medicine, University of California San Francisco, San Francisco, CA, USA; <sup>11</sup>Gustave L. and Janet W. Levy Library, Icahn School of Medicine at Mount Sinai, New York, NY, USA; <sup>12</sup>Division of Gastroenterology and Hepatology, Loma Linda University Health, Loma Linda, CA, USA.

### ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Arpan A. Patel, M.D., Ph.D.  
1100 Glendon Avenue, Suite 850, Room 810  
Los Angeles, CA 90024, USA

E-mail: arpanpatel@mednet.ucla.edu  
Tel.: 310-267-4498

1. Physical Symptom Burden
2. Psychological Symptoms
3. Social, Religious, and Spiritual Aspects of Care
4. Caregiver Burden
5. Advance Care Planning
6. Liver Transplantation
7. Health Care Use
8. End of Life Care

**FIG. 1.** Palliative care domains of interest included in literature search.

Team members (A.P., C.W., N.N.U., L.H., M.R.) reviewed the search results for each domain to identify empirical research studies published in English on the topic. Any articles that were not classified as original research, such as narrative reviews or letters to the editor, were excluded. Citations were then assigned to other reviewers by domain and further excluded based on abstract and full-text review. To identify additional relevant studies, the references of all articles identified by the searches were reviewed and additional citations were included if they were deemed relevant (Fig. 2). Separate literature reviews were then conducted in groups for each domain. Eight domains were condensed to five final domains due to overlapping themes. Multiple meetings were held to present reviews, identify critical gaps in current research, and suggest relevant future work that can address these gaps.

## Results

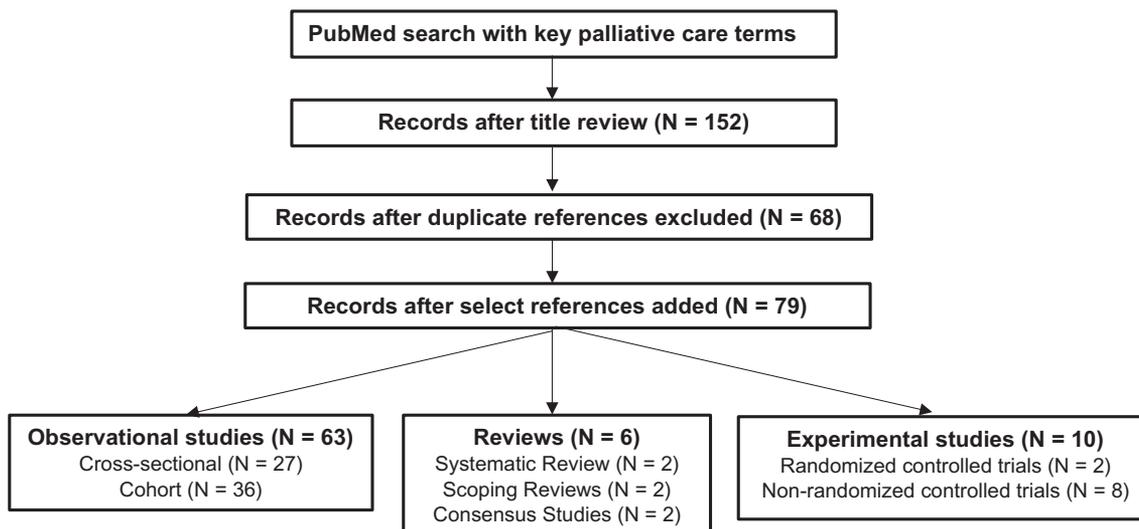
A total of 79 studies were included in this review, consisting of 63 observational, six review, and 10 experimental studies (Fig. 2). We present the case of a patient with AdvLD throughout this section to illustrate how different domains of PC become relevant to care throughout the illness trajectory.

### CASE STUDY, PART 1

Mr. Smith is a 55-year old man with obesity, hypertension, and insulin-dependent type II diabetes who was diagnosed with cirrhosis incidentally during a routine laparoscopic cholecystectomy. He developed new ascites postoperatively and received an abdominal paracentesis and oral diuretics during his hospitalization. He comes to your office to establish care. He is accompanied by his wife. He has frequent lower extremity cramps and fatigue as well as mild depression. He rates his overall quality of life as poor.

### Pain and Physical Symptoms

A total of 16 studies, including 10 observational, three review, and three experimental studies pertained to this domain. Pain is a frequent symptom experienced by patients with DC and HCC. The most common locations for pain reported by patients with DC are the abdomen and back.<sup>(27-29)</sup> Pain has a significant impact on general activity and intensifies toward the



**FIG. 2.** Flow diagram for literature review.

end of life.<sup>(30-34)</sup> Several tools that have been validated in other chronic illness populations have been used to assess pain in patients with AdvLD, including the Brief Pain Inventory, Edmonton Symptom Assessment Scale, McGill Pain Questionnaire, self-care behavioral log, and Memorial Symptom Assessment Scale. Several reviews have been published on choice of analgesic agents for DC and HCC.<sup>(35-38)</sup> Polypharmacy, particularly with opiates, is common for pain control among patients with DC. Despite this, less than half reported adequate symptom relief.<sup>(27,31,39)</sup>

Other debilitating symptoms, such as muscle cramps, insomnia, erectile dysfunction, breathlessness, fatigue, pruritus, dyspepsia, lower urinary tract symptoms, nausea, and poor appetite, are present in over a third of patients with DC.<sup>(27)</sup> Patients with HCC also report many of these symptoms while undergoing treatments and toward the end of life.<sup>(30,40,41)</sup> Patients with DC rate edema, ascites, encephalopathy, concentration and memory impairment, itching, muscle cramps, falls, and medication side effects as having the most impact on their daily lives.<sup>(6)</sup> No comparative effectiveness studies of different pharmacologic and nonpharmacologic interventions for nonpain symptoms were found.

Inpatient specialty PC services are infrequently involved in symptom management for patients with liver disease, which may explain discomfort among PC teams in how to treat pain in these patients.<sup>(42-44)</sup> However, there is only one report of an early specialty PC intervention at the time of liver transplant evaluation in patients with DC that was effective in improving physical well-being, pruritus, anxiety, appetite, and fatigue.<sup>(45)</sup>

## Psychological and Social Well-Being

A total of 19 studies, including 14 observational, two review, and three experimental studies pertained to this domain. Depression, anxiety, and posttraumatic stress disorder are common in patients with AdvLD, although the use of different measurement tools likely has led to wide heterogeneity in reported frequencies.<sup>(27-29)</sup> Mental health appears to be more dynamic than control of physical symptoms throughout a patient's illness trajectory.<sup>(30,32)</sup> Higher levels of depression are associated with higher rates of unmet supportive needs and uncertainty about illness, and rates of suicidality tend to be higher among patients with cirrhosis than the general population.<sup>(46-48)</sup> Patients with AdvLD and their

caregivers note major disruptions in their personal and family lives, particularly as their illnesses worsen.<sup>(30,32,49)</sup> Major social burdens faced by patients include financial costs, limited social support, active or former substance use, stigma of having liver disease, impaired sexual health, and perceived burden on other family members.<sup>(6,33,50-52)</sup> Demographic surrogate measures of poor social support, such as lower socioeconomic status, single status, and active substance use, have also been associated with reduced survival, unmet supportive needs, and lower access to supportive care services in patients with AdvLD.<sup>(48,53,54)</sup> Despite a high need, patients with DC and HCC have poor access to mental health services.<sup>(33,50)</sup> To the best of our knowledge, there are no major literature syntheses that have examined the impact of pharmacologic and nonpharmacologic treatments on mental health in patients with DC and HCC. Mindfulness-based stress reduction (MBSR) and early PC interventions in the outpatient and inpatient settings have been associated with lower depression scores in patients with AdvLD. MBSR was also effective in improving social well-being for patients with DC in these small studies.<sup>(45,55,56)</sup>

## CASE STUDY, PART 2

A few months later, Mr. Smith is admitted for an esophageal variceal bleed and receives successful band ligation in the intensive care unit (ICU). He is discharged home for a brief period but develops peritonitis, requiring a prolonged course of intravenous antibiotics. He comes to your clinic after spending a month at a subacute rehabilitation facility. His Model for End-Stage Liver Disease–Sodium (MELD–Na) is 14. His ascites and esophageal varices are well managed, but his wife quit her job in order to provide more support at home. Both of them express uncertainty about what to expect moving forward.

## Caregiver Burden

A total of 19 studies, including 14 observational and five experimental studies pertained to this domain. Informal (or unpaid family) caregivers tending to patients with AdvLD face significant burdens and challenges. Spouses are the most frequent informal caregivers for patients being evaluated for liver transplantation.<sup>(57)</sup> Informal caregivers of patients with terminal HCC report feeling unprepared and uncertain

about their loved ones' illness, wanting more medical information and searching for cures.<sup>(30,49)</sup> Caregivers of patients with DC report feeling overwhelmed in the setting of hepatic encephalopathy and note difficulty in navigating practical issues related to access to health services and supportive care. They also report reductions in their own physical health and difficulty coping at the end of life of their loved ones.<sup>(32,33,49,52,58)</sup> When patients with AdvLD become critically ill, families report different perceptions of how sick their loved one was compared to the medical team; informal caregivers often feel that prolonging life was the only option. This may be due to receiving incomplete medical information.<sup>(59)</sup> They report high rates of mood disturbance and strain as well as lower quality of life and life satisfaction, both before and after liver transplantation. Depressive symptoms in caregivers may correlate with presence of encephalopathy and higher MELD.<sup>(60-62)</sup> The burden of caring for patients with AdvLD may also be associated with increased rates of hazardous alcohol consumption and financial hardship, particularly among African Americans and women.<sup>(63)</sup> Caregivers of patients with AdvLD report significant financial burden related to caring for their loved ones, with over double the number of informal caregiver hours and costs as age-matched older adults.<sup>(64-66)</sup>

Intervention studies targeting caregivers are sparse. One intervention looked at the effect of a telephonic uncertainty self-management intervention for patient-caregiver dyads awaiting liver transplantation, but outcomes were no different between patients receiving and not receiving the intervention.<sup>(67)</sup> Another study showed reductions in caregiver burden among patients and their caregivers who participated in a brief MBSR and supportive group therapy program.<sup>(55)</sup> A few small PC interventions have also been effective. A nurse-led PC intervention was not only feasible but led to a reduction in symptom burden and improved quality of life for informal caregivers.<sup>(68)</sup> In one study investigating a PC-led ICU intervention for critically ill patients with AdvLD, family satisfaction was higher with overall care, symptom management, and end-of-life management for patients receiving the intervention, although low response rate was an important limitation of the study.<sup>(69)</sup>

## Advance Care Planning

A total of 23 studies, including 19 observational, two review, and two experimental studies pertained

to this domain. In addition to better symptom control, patients with HCC and their caregivers report wanting to know more about how presence of these symptoms fit into the context of their overall disease trajectory and prognosis.<sup>(50,70,71)</sup> A systematic review of 19 qualitative and quantitative studies found that patients with AdvLD and caregivers have unmet informational needs about their prognosis and supportive care in primary care and hepatology practice settings.<sup>(72)</sup> Gaps in discussing advance directives have been reported by gastroenterology fellows.<sup>(73)</sup> There is a lack of concordance between what patients prioritize as concerns about their cirrhosis (developing liver cancer, losing ability to do daily tasks, fear of dying, fear of the unknown) compared to what health professionals focus on during visits.<sup>(33,50)</sup> This lack of communication is seen across practice settings from ambulatory practices to ICUs where patients and families face decisions about life-sustaining treatments.<sup>(59)</sup> The fact that few patients have advance directives or any conversation with providers regarding goals of care (GOC) makes it largely unclear whether the care they receive throughout their disease trajectory or at the end of life is concordant with their goals.<sup>(29,50,74,75)</sup>

Advance care planning (ACP) is a process that supports adults at any age or stage of health in understanding and sharing their personal values, life goals, and preferences regarding future medical care and end-of-life care. It is also considered an important metric in providing high-quality PC for patients with AdvLD.<sup>(76)</sup> Qualitative studies of patients with AdvLD have revealed that patients have a poor understanding of their prognosis and of the overall ACP process. This uncertainty about prognosis hampers patients' abilities to be informed about their condition and plan for the future, and this concern is also shared by liver specialists.<sup>(52,77)</sup> Eligibility of patients to be on the transplant wait list may also be a barrier to ACP. A majority of hepatologists believe that patients on the transplant wait list should be "full code"; they report more discomfort with including PC services in discussions about prognosis and ACP documentation when patients are transplant eligible compared to ineligible patients.<sup>(78,79)</sup> Lower levels of comfort with performing ACP and managing expectations, lack of continuity of care, and misperceptions about PC services all contribute to low rates of ACP.<sup>(28,80,81)</sup> For instance, in one single-center study, an overwhelming majority of attending transplant hepatologists

misperceived PC as being synonymous with end-of-life care.<sup>(82)</sup> Others seem to fear that PC discussions might diminish hope and perseverance among those listed or being evaluated for liver transplant.<sup>(78,79,81)</sup> Such fears that discussions might cause loss of hope, feelings of abandonment, or result in the patient choosing to discontinue aggressive care, such as transplant, have been demonstrated in qualitative studies as well.<sup>(28)</sup> There are, however, no studies that have shown an association between early PC interventions and loss of hope. GOC discussions still appear to be the most common reason for inpatient PC consultation.<sup>(42)</sup> However, among patients who were evaluated but denied liver transplantation, only 11%-34% received PC consultation, and this occurred only 1-2 weeks before death.<sup>(29,83,84)</sup> Patients have reported that ideally they prefer ACP discussions that are held outside of periods of acute illness with providers they have familiarity with.<sup>(77)</sup> Two quality improvement initiatives featuring outpatient PC consultation and feasible system-related changes in a hepatology clinic led to improved documentation of ACP.<sup>(45,85)</sup>

### CASE STUDY, PART 3

Mr. Smith is readmitted to the hospital for encephalopathy and is found to have a bacterial pneumonia requiring mechanical ventilation and renal dysfunction requiring hemodialysis. While he is hospitalized, his MELD-Na rises to 36, so he is transferred to a center offering liver transplantation but is not wait-listed due to his acute illness, comorbidities, and frailty. After remaining on vasopressors and intubated for a week without much clinical improvement, the ICU team requests a specialty PC consultation. During GOC discussions, Mr. Smith's wife mentions that it was her husband's wish to die peacefully at home. She soon learns that this is not a realistic option and remorsefully chooses comfort-focused measures. Mr. Smith receives a palliative extubation and passes.

### End of Life Care

A total of 36 studies, including three review and 33 observational studies pertained to this domain. At the end of life, 61%-78% of patients with DC and 58% of Medicare beneficiaries with HCC not enrolled in hospice die in the hospital.<sup>(86-91)</sup> During these long inpatient stays, greater than 50% of patients with

AdvLD receive mechanical ventilation, 16% receive dialysis, and 43% receive a blood transfusion, while 28% of patients with HCC use ICU care at the end of life.<sup>(90,92)</sup> Quality indicators for end-of-life care in patients with AdvLD include 1) adequate control of symptoms (pain and dyspnea) and 2) presence of GOC discussions that clarify surrogate decision makers and assure that care received is consistent with the patient's goals.<sup>(76)</sup> Unfortunately, both patients with DC and HCC report having poorly controlled pain, dyspnea, confusion, poor functional status, and depression at the end of life.<sup>(30,32,65,93)</sup>

Several studies suggest poor communication between providers, patients, and their families during the terminal phase. Families of patients listed for liver transplant reported infrequent conversations about prognosis and life-sustaining treatment decisions.<sup>(94)</sup> Among patients with AdvLD who died during an index hospitalization, 96% believed they had a greater than 75% chance of surviving the next 2 months,<sup>(65)</sup> despite national data from U.S. hospitalizations suggesting that only 10% of patients with AdvLD receiving cardiopulmonary resuscitation survive until hospital discharge and only 3% are able to make it home.<sup>(95)</sup> Studies investigating treatment preferences for patients with HCC at the end of life have not been published.

Specialty PC consultation has been associated with improved quality of end-of-life care. In one study, 104 listed liver transplant recipients admitted to a surgical ICU underwent a structured PC intervention program (PC consultation within 24 hours of admission, interdisciplinary family meeting within 72 hours, ongoing PC educational modules for transplant providers). PC intervention resulted in an increase in GOC discussions, earlier do-not-resuscitate status, and decreased ICU length of stay.<sup>(69)</sup> Another study suggested that offering simultaneous hospice and liver transplant care is feasible. In this study, 157 patients with DC with a MELD greater than 25 were enrolled in hospice, 8 of whom were listed for liver transplantation. Of the listed patients, 6 received hospice services up until the time of liver transplantation (with a median hospice length of stay of 81 days).<sup>(96)</sup> PC and hospice use are associated with significant reductions in health care costs for patients with AdvLD.<sup>(97)</sup> At the end of life, PC is associated with \$10,000 less spent per hospitalization for patients with DC.<sup>(92)</sup> In patients with HCC, high health care costs have been

attributed to terminal hospitalizations and high use during these admissions. Two studies from Taiwan showed that hospice enrollment is associated with lower likelihood of high health care costs without any impact on survival.<sup>(64,98-101)</sup> Procedure burden is significantly lower for patients receiving either PC or hospice.<sup>(90,92,102)</sup> Both PC use and hospice enrollment are also associated with lower rates of readmission and hospitalization.<sup>(90,103)</sup> Although qualitative studies have suggested burdensome experiences for patients and families in the absence of supportive services at the end of life, studies that qualitatively examine the specific benefits provided by PC services and hospice are lacking for AdvLD.<sup>(28,30,32,33,70,94,104,105)</sup>

Despite these benefits, specialty PC services are infrequently used during hospitalizations before (4.5%-5.6%) and at the end of life (30%) for patients with DC.<sup>(53,90)</sup> Thirty-eight percent of patients hospitalized with HCC receive PC at the end of life.<sup>(54,92,103)</sup> Hospice is similarly underused. Only 6% of patients with DC (and 36% of Medicare beneficiaries) enroll in hospice at the end of life as opposed to 46%-73% of patients with HCC.<sup>(90,106)</sup> However, in studies where timing of PC and hospice use could be measured, referrals were often made close to the time of death.<sup>(29,83,84,90,107,108)</sup> Specific patient, family, and provider barriers to hospice use have not been published.

## Critical Gaps in Current Research

Based on our summaries of the literature, we identified critical gaps in research that should be addressed so that effective sustainable interventions to improve PC can be developed (Table 1). A few of the PC domains we reviewed are well described, such as pain, physical symptom burden, and psychological symptoms. Our knowledge of other PC domains, such as informal caregiver burden, ACP, and social well-being, is less detailed. More fundamental understanding with regards to how these domains affect patients and their caregivers is needed. Lastly, several key PC domains (physical symptoms, psychological well-being, caregiver burden, social well-being, and ACP) use instruments that may require further validation for patients with AdvLD. Most studies have only used tools developed for other chronic illness populations.

## High-Priority Questions for Future Research

Based on our literature review, we selected the following questions to help guide future steps in PC research:

Q1. What interventions (pharmacologic and non-pharmacologic) are most effective at improving pain and other physical symptoms, and what instruments are practical for tracking this progress? (Pain and Physical Symptoms)

Q2. What interventions (pharmacologic and non-pharmacologic) are most effective for supporting psychological health and social well-being, and what instruments are practical for tracking this progress? (Psychological and Social Well-Being)

Q3: What are the most important priorities and areas of improvement needed for caregivers caring for patients with AdvLD? (Caregiver Burden)

Q4. How well do patients with AdvLD and caregivers understand prognosis throughout the illness trajectory, and what effect do prognostic awareness and provider quality of communication have on end-of-life care, particularly life-sustaining treatment decisions? What interventions are effective? (Advance Care Planning, End-of-Life Care)

Q5. How feasibly and acceptably can PC assessments, either by specialists or nonspecialists, be integrated into transplant and nontransplant settings? (All Domains)

We have highlighted examples of methodologic approaches that can be used to answer these questions (Table 1). Structured literature reviews, such as systematic reviews and meta-analyses, are needed to identify and summarize high-quality effective interventions used to treat physical (Q1) and psychological (Q2) symptoms. For other domains, it is critical to develop effective interventions for patients and caregivers that can be translated to clinical care. One barrier is the lack of validated instruments for measuring outcomes, such as symptom control (Q1, Q2) and caregiver burden (Q3). Current instruments should be field tested in patients with AdvLD with appropriate psychometric testing.<sup>(109)</sup> Cognitive interviews and focus groups

**TABLE 1. HIGH-PRIORITY QUESTIONS FOR PALLIATIVE CARE RESEARCH IN ADVANCED LIVER DISEASE**

Domain(s)	Critical Gaps	High Priority Questions	Example Future Work
Pain and physical symptoms	Poor understanding of best interventions for treating pain and nonpain physical symptoms	Q1. What interventions (pharmacologic and nonpharmacologic) are most effective at improving pain and other physical symptoms, and what instruments are practical for tracking this progress?	Systematic review and meta-analyses; validation of known instruments using cognitive interviews in patients with AdvLD
Psychological and social well-being	Poor understanding of best interventions for supporting psychological health and social well-being	Q2. What interventions (pharmacologic and nonpharmacologic) are most effective for supporting psychological health and social well-being, and what instruments are practical for tracking this progress?	Systematic review and meta-analyses; validation of known instruments using cognitive interviews in patients with AdvLD
Caregiver burden	Insufficient knowledge of what drives caregiver burden	Q3. What are the most important priorities and areas of improvement needed for caregivers caring for patients with AdvLD?	Data collection using both quantitative and qualitative methods to assess caregiver outcomes with instruments and semistructured interviews
Advance care planning and end-of-life care	Unclear whether ACP affects end of life outcomes. Lack of data on how patients and caregivers perceive prognosis and goals of care discussions	Q4. How well do patients with AdvLD and caregivers understand prognosis throughout the illness trajectory, and what effect do their prognostic awareness and provider quality of communication have on end-of-life care, particularly life-sustaining treatment decisions? What interventions are effective?	Longitudinal data collection with patient and caregiver surveys; measurement of bereaved family survey and end-of-life outcomes; qualitative and quantitative data collection for quality of communication
All domains	Little data on how to practically integrate PC principles into management of AdvLD	Q5. How feasibly and acceptably can PC assessments, either by specialists or nonspecialists, be integrated into transplant and nontransplant settings?	Surveys with closed and open-ended elements to health care providers treating patients with AdvLD

can be used to further refine instruments; this has previously been done to validate quality of life instruments for patients with liver disease and can similarly be used for more specific PC outcomes.<sup>(110,111)</sup> More observational longitudinal data are needed to better understand caregiver burden (Q3), ACP (Q4), and end-of-life care (Q4) from the perspectives of patients and caregivers. Similarly, perspectives of providers are needed to better understand the feasibility of incorporating PC assessments (Q5). Ideally, research that attempts to clarify these phenomena should strive to include mixed methods, which involve collection and synthesis of both quantitative and qualitative data. Although most peer-reviewed medical literature solely features quantitative data, qualitative data obtained from observations, interviews, or focus groups can be used to capture the “what,” “how,” and “why” of phenomena, which can be used to better answer research questions.<sup>(112)</sup> A recent example of mixed methods being incorporated in PC research in liver disease is the ongoing National Institute of Nursing Research-funded study, entitled “Symptom burden in end-stage liver disease patient-caregiver dyads.” This investigation aims to understand the trajectory of physical and psychological symptom burden in patients with AdvLD and their caregivers. In the study, symptom

burden is measured using both survey instruments as well as telephone-based interviews with open-ended questions.<sup>(113)</sup> Another investigation is a multicenter, cluster-randomized, comparative effectiveness study comparing PC delivered by PC specialists versus hepatologists, funded by the Patient Centered Outcomes Research Institute. In addition to the trial, semistructured interviews will be performed to capture patient/caregiver and health care provider experiences.<sup>(114)</sup> In both settings, qualitative data collection allows investigators to better explain their quantitative results.

## Conclusion

In this paper, we have summarized the state of the literature with regards to PC outcomes in patients with AdvLD. We found that the burden of supportive needs, such as physical symptoms, mental health, social well-being, caregiver needs, advance care planning, and end-of-life care, are high. With iterative input from a multidisciplinary and multispecialty panel of experts, we have established priorities for PC research based on these findings. With this publication, we hope to inspire future collaborative work that is informative and impactful. In fields where discovery, dissemination,

and implementation need to be accelerated in order to meet the needs of our patients, it is important for both the clinical and research communities to see the unique value added by PC to improve quality of life for patients living with AdvLD and their families.

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Author names in bold designate shared co-first authorship.

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