

Nonhospice Palliative Care Within the Treatment of End-Stage Liver Disease

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Palliative care (PC) that has evolved from a focus on end-of-life care to an expanded form of holistic care at an early stage for patients with serious illnesses and their families is commonly referred to as nonhospice PC (or early PC). Patients with end-stage liver disease (ESLD) suffer from a high symptom burden and a deteriorated quality of life (QOL), with uncertain prognosis and limited treatment options. Caregivers of these patients also bear an emotional and physical burden similar to that of caregivers for patients with cancer. Despite the proven benefits of nonhospice PC for other serious illnesses and cancer, there are no evidence-based structures and processes to support its integration within the routine care of patients with ESLD and their caregivers. In this article, we review the current state of PC for ESLD and propose key structures and processes to integrate nonhospice PC within routine hepatology practice. Results found that PC is highly underutilized within ESLD care, and limited prospective studies are available to demonstrate methods to integrate PC within routine hepatology practices. Hepatology providers report lack of training to deliver PC along with no clear prognostic criteria on when to initiate PC. A well-informed model with key structures and processes for nonhospice PC integration would allow hepatology providers to improve clinical outcomes and QOL for patients with ESLD and reduce health care costs. Educating hepatology providers about PC principles and developing clear prognostic criteria for when and how to integrate PC on the basis of individual patient needs are the initial steps to inform the integration. The fields of nonhospice PC and hepatology have ample opportunities to partner clinically and academically. (HEPATOLOGY 2020;71:2149-2159).

End-stage liver disease (ESLD) is the 12th leading cause of death and claims approximately 66,000 lives each year in the United States.⁽¹⁾ Between 2006 and 2016, the prevalence of ESLD increased by 7.9% among men 25-34 years of age and 11.4% among women in the same age group because of the increasing burden of nonalcoholic steatohepatitis, alcohol-associated liver disease, and advanced hepatitis C virus.⁽²⁾ In parallel, mortality due to ESLD increased by 65% from 1999 to 2016.⁽³⁾

ESLD is also associated with functional and cognitive impairment, often with concomitant mental health and substance use disorders. The physical and psychological symptom burden and social-role

consequences of ESLD are often worse than those for many non-liver cancers.⁽⁴⁾ The most frequently reported symptoms include pain, breathlessness, muscle cramps, sleep disturbance, fatigue, pruritus, anxiety, depression, and erectile dysfunction.⁽⁴⁾ In addition to its direct effects on patients, ESLD is linked with a substantial caregiver emotional and physical burden, mirroring that observed in caregivers of patients with cancer.⁽⁵⁾ However, interventions to improve the quality of life (QOL) for patients with ESLD and their caregivers are underdeveloped.

Palliative care (PC) is the most promising solution to address the physical, psychological, and caregiver burdens of ESLD. The aim of PC is to provide holistic

Abbreviations: ACP, advance care planning; ESLD, end-stage liver disease; LT, liver transplantation; PC, palliative care; QOL, quality of life; SICU, surgical intensive care unit.

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care for patients with serious illnesses and their families, focusing on symptom management, goals-of-care discussions, advance care planning (ACP), and end-of-life care or hospice care. Whereas hospice care is considered for patients with a projected life expectancy of less than 6 months, nonhospice PC is inclusive of all the other elements of PC applicable from the time of diagnosis onward for any serious illness.⁽⁶⁾ Nonhospice PC has been clearly defined recently (Table 1). Unfortunately, there is a suboptimal understanding of the structures and processes required to integrate nonhospice PC within hepatology. The goal of this review is to synthesize recent literature regarding the current state of PC for patients with ESLD and propose key structures and processes required to integrate nonhospice PC within hepatology practice.

PC Overview

PC is a subspecialty focusing on patients' individual needs (including physical, psychosocial, and spiritual needs). Early PC has been shown to improve patient symptoms, QOL, patient satisfaction, and ACP discussions and reduce health care costs and usage,

TABLE 2. The Role and Benefits of Nonhospice PC

Nonhospice PC Roles	Potential Benefits
Symptom management (physical and psychological)	Improved symptom control and reduced suffering
Distress management	Improved QOL
Spiritual and cultural care	Improved support for patients and caregivers; better coping with illness; improved communication
Disease and prognosis understanding	Better understanding of disease and preparedness to face the normal trajectory of illness
ACP and goals of care	Establishment of advance directives and surrogate decision-makers; decreased aggressive care at the end of life; increased hospice use when needed
Care coordination (among providers, offering community support through social-work services)	Decreased health care use and health care costs; improved quality of care
Caregiver support	Reduced caregiver burden; improved satisfaction with care; bereavement support

Abbreviations: ACP, advance care planning; PC, palliative care; QOL, quality of life.

particularly in regard to intensive medical care and the caregiver burden (Table 2).⁽⁷⁾ More recently, several noncancer societies have recommended early introduction of PC for chronic illnesses such as end-stage renal disease, heart failure, and lung disease⁽⁸⁾; however, no such guidelines exist in the liver-disease literature.⁽⁹⁾

Current State of PC for ESLD

Several studies within the past 5 years identified limited availability of PC services for patients with liver disease, leading to limited and late involvement of PC

TABLE 1. Definitions of Nonhospice PC

Organization	Definition
CAPC (2017) ⁽⁴⁹⁾	"Specialized medical care for people with serious illness that is focused on providing relief from symptoms and stress of a serious illness with the goal of improving quality of life for both the patient and the family"
National Consensus Project clinical practice guidelines for quality PC (2018) ⁽⁵⁰⁾	"Patient and family-centered care that optimizes quality of life by anticipating, preventing and treating suffering"

Abbreviations: CAPC, Center to Advance PC; PC, palliative care.

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specialists, by which many potential benefits of PC may be lost.⁽¹⁰⁾ In an analysis of a nationwide inpatient sample, Rush et al.⁽¹¹⁾ found that only 4.5% of all ESLD-related admissions received a PC consultation, although this increased from 1% in 2006 to 7.1% in 2012. Barnes et al.⁽¹²⁾ found that only 19% of eligible patients (defined as having ≥ 2 admissions within 6 months for decompensated cirrhosis, excluding those who were listed for liver transplantation [LT]) received “early PC” (i.e., as defined by, PC received > 30 days before death), with hospitalization costs significantly reduced in those with early PC because of a lower number of endoscopies and blood transfusions. Similarly, studies have shown that less than 20% of patients removed from the LT waiting list received a PC consultation, and most of those occurred within 72 hours of death in an inpatient setting.⁽¹³⁾ A provider survey conducted among veterans’ practices found that despite 82%–88% of practices having PC available on site, less than 25% of patients with ESLD were referred for PC consultation.⁽¹⁴⁾ Commonly reported barriers were insufficient staff knowledge about PC, uncertainty of timing to make PC referrals, and patient refusal to receive PC (potentially because of the misconception of PC being equivalent to end-of-life care). A study from Canada reported that less than 20% of patients with cirrhosis had ACP documented, despite a public campaign to raise awareness of ACP within the province, and almost 66% of patients were listed as being full-code patients despite a dismal prognosis.⁽¹⁵⁾ However, patients preferred to have ACP discussions when they were still well, rather than waiting until their health completely declined, and with the physicians with whom they had ongoing relationships, such as their hepatologists.

Few prospective studies have tested nonhospice PC for ESLD, and some are ongoing (Table 3). Of the few prospective studies, 50% are single-arm uncontrolled studies. Only one randomized controlled trial (RCT) has been completed, but that was terminated because of under-enrollment. However, all studies have supported feasibility and positive patient outcomes.

Barriers to Implementing PC

Barriers to include PC within routine hepatology practice can be categorized into those related to patients, providers, and health systems.

1. Many patients see PC as being synonymous with end-of-life care. The fear that PC may exclude them from LT candidacy makes patients and their caregivers less willing to receive a PC consultation. Hepatic encephalopathy can make the patients unable to participate in PC discussions, such as goals-of-care or ACP discussions.⁽²³⁾
2. For providers, barriers include uneasiness in including PC consultants, misperception of PC being just end-of-life care, insufficient guidelines for PC integration, inadequate access to PC providers coupled with deficiency in the PC-provider workforce, insufficient time during routine clinical care for complex discussions, inadequate training in goals-of-care discussions or psychological/symptom management, and a preferential focus on life-saving interventions.⁽²⁴⁾ Fear of upsetting patients, not wanting to abandon them, considering PC referral as an admission of failure/no hope, patients’ having impaired cognitive capacity to participate in provider-led discussions, and providers not completely understanding the benefits of PC are other reasons.⁽⁴⁾
3. For health systems, implementation and policy barriers have been identified.⁽²⁵⁾ Implementation barriers include limited number of providers with PC training, challenges in identifying patients for appropriate PC referral at the systems level, and need for a culture change across settings. Policy barriers include fragmented health care systems, lower profit margins in reimbursements for PC services, need for a preauthorization in some states and for some insurance carriers, inability to cover the uninsured, and a lack of complete evidence to drive this change. However, given the move of U.S. health care toward patient-centered care, health systems are looking for options to improve patient satisfaction, and PC has proven to be one of them.

Structures and Processes Required for Integrating Nonhospice PC for ESLD

Models of nonhospice PC differ in their levels of integration (e.g., freestanding or embedded PC

TABLE 3. Recent Prospective Nonhospiice PC Intervention Studies for ESLD Population

Author/Study (Year)	Study Design/ Location	Sample Size	Population	PC Intervention (Comparators)	Primary Outcome	Secondary Outcomes	Results
Verma et al. PAL LIVER study (2019) ⁽¹⁶⁾	Cluster RCT, multisite/U.S.	Projected n = 1,260 patient-caregiver dyads	ESLD (with complications within 6 months) including HCC	Comparative-effectiveness research of 2 PC models: trained hepatologist-led PC vs. consultative PC	QOL (Fact-HEP)	Symptom burden, distress, caregiver burden, and QOL; health care use, goal-concordant care, end-of-life care	Ongoing
Shindal et al. COMPASS trial (2019) ⁽¹⁷⁾	RCT/U.S.	N = 63	Inpatients with ESLD	Inpatient specialist PC consultations + outpatient follow-up by a PC nurse vs. standard care	Time until first readmission	Days alive outside hospital, referral to hospice, death, readmissions, QOL, depression, anxiety, and quality of end of life	Stopped before enrollment intervention group had lower hazard of readmission and greater odds of having more days alive outside the hospital
Chung, ACP decision support tool (2018) ⁽¹⁸⁾	RCT/U.S.	Projected n = 50	ESLD (ineligible for LT), H/O hospitalization	ACP videos vs. narrative description by a research assistant	Feasibility	Patient knowledge, end-of-life care, ACP discussions	Ongoing
Wray, Early PC for HCC (2019) ⁽¹⁹⁾	RCT/U.S.	Projected n = 72	Advanced HCC	Early PC consultation (at time of HCC diagnosis) vs. standard care/no PC	QOL	Survival, resource use, cost use	Ongoing
Kimbell et al. (2018) ⁽²⁰⁾	Single-arm feasibility trial/Scotland/ UK	47 patients, 23 caregivers, 13 case-linked professionals	Decompensated cirrhosis with unplanned hospitalization, not transplantation eligible	Liver nurse specialist trained in primary PC delivered the intervention after hospital discharge, for 6 months	Mixed-methods feasibility assessment	PC outcomes and QOL	High patient and provider acceptability; improved QOL
Hansen et al. (2017) ⁽²¹⁾	Single-arm longitudinal study/U.S.	Projected n = 200 patient-caregiver dyads	ESLD	Tailored PC intervention	Change in symptoms and QOL in patients and caregivers	Predictors of types of patient-caregiver dyads that would benefit from tailored PC interventions	Ongoing
Hudson et al. (2017) ⁽²²⁾	Single-arm quality improvement study/ UK (development and implementation of a prognostic tool)	n = 73	Inpatients with decompensated cirrhosis	Prognostic screening coupled with supportive care intervention	Feasibility in routine care	Validation of prognostic tool	A model of integrated PC coupled with a prognostic toolkit for inpatient cirrhosis care
Bauman et al. (2015) ⁽⁶¹⁾	Single-arm quality improvement study/U.S.	n = 50	Patients with ESLD awaiting LT	Early PC by a PC provider and research nurse	Symptom control	Depression and mood	50% of moderate-to-severe symptoms improved; 43% of patients had improvement in depression

Abbreviations: ACP, advance care planning; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; ESLD, end-stage liver disease; Fact-HEP, Functional Assessment of Cancer Therapy–Hepatobiliary Cancer; H/O, history of; HCC, hepatocellular carcinoma; LT, liver transplantation; PAL LIVER, Palliative Care for Liver Diseases; PC, palliative care; QOL, quality of life; RCT, randomized controlled trial; U.S., United States.

clinics, inpatient PC consultation, or a dedicated inpatient PC unit) and place of delivery of PC (e.g., inpatient, outpatient, home-based, or remote/using telehealth). Table 4 outlines the model structures and their potential strengths and weaknesses. Timely, integrated PC requires contact at a time when the patients are functional, independent, and have supportive care needs. This is not a prognosis-based decision; rather, it is a decision based on patient or family-caregiver needs. This type of care has been shown to be most effective at the time of outpatient visits, making outpatient clinics an ideal setting for nonhospice PC.⁽²⁰⁾ However, many different models exist that are tailored to overcome geographic barriers, workforce shortages, and so on (e.g., virtual clinics, telehealth).

The structures and processes to enable the heterogeneous PC models may vary. However, there are basic elements that must be the part of a PC intervention.⁽²⁶⁾ These elements include patient-centered and family-centered care, an interprofessional team, provider characteristics, screening tools, goals-of-care discussions, ACP, concurrent care models, and caregiver support.

PATIENT-CENTERED AND FAMILY-CENTERED CARE

Patient-centered care, defined as health care that is inclusive of informed, respected, and involved patients, is one of the six key elements of high-quality care according to the Institute of Medicine.⁽²⁷⁾ Optimal nonhospice PC engages patients and caregivers in decision-making, prognosis-understanding, and preparedness for acute-decompensation events. An example is the ENABLE model (Educate, Nurture, Advise, Before Life Ends), which has demonstrated effectiveness for oncology and heart failure.⁽²⁸⁾ The intervention included an in-person PC assessment and weekly telehealth coaching sessions with advanced-practice nurses for 6 weeks and 4 weeks for caregivers on select topics such as problem-solving, symptom management, communication, and decision-making. The qualitative programmatic evaluation found that participants gained illness management and decision-making skills while continuing with curative treatments, reported feeling empowered, and experienced better care planning.⁽²⁹⁾

INTERPROFESSIONAL TEAM

PC assessments target the physical, psychological, social, spiritual, and cultural needs of patients. An interprofessional team, usually comprising a PC physician, a nurse practitioner, a registered nurse, a social worker, psychologists, and chaplains, is needed to tackle the multidimensional needs of patients and caregivers.⁽²⁹⁾ Team efficiency features good leadership, effective decision-making, and communication among team members. There is no evidence available to determine which discipline optimizes the efficacy of PC. Interprofessional PC teams have improved patients' health outcomes (such as symptoms and survival); however, no study has compared the use of interprofessional teams with a solo-practitioner approach.⁽³⁰⁾

PROVIDER CHARACTERISTICS

Conventionally, a trained PC specialist provides PC when consulted and is often referred to as "specialist/consultative PC." However, given the shortage of PC providers, the high value and demand of PC, and the need to reduce care fragmentation, the concept of primary PC has gained importance. This includes basic skills that all clinicians should have (i.e., basic management of pain and symptoms; depression and anxiety; and basic discussions on prognosis, goals of care, suffering, and code status).⁽³¹⁾ Web-based PC training has been described as a pragmatic approach, given the time constraints of most providers, and has demonstrated enhanced patient care.⁽³²⁾ A study testing an online curriculum demonstrated improved confidence, knowledge, and satisfaction among primary care providers offering PC to their patients.⁽³³⁾ An RCT demonstrated improved patient symptoms in the group receiving PC from primary care physicians trained in PC versus primary physicians not trained in PC.⁽³⁴⁾ Similar results have been seen specialists trained in PC. For example, a nephrologist-led PC study showed a significant increase in documentation of patient preferences for cardiopulmonary resuscitation and limits on life-sustaining treatment.⁽³⁵⁾

It is expected that hepatologists are aware of patient prognosis and treatment options, whereas PC specialists may not be fully aware of those including transplantation eligibility, which can change over time. With appropriate training, hepatologists can provide

TABLE 4. Models of PC: Strength and Weaknesses

Model	Description	Strengths	Weaknesses
1. Outpatient PC clinics (freestanding)	PC providers (M.D., N.P., R.N.) conduct standalone PC clinics	<ol style="list-style-type: none"> 1. Continuity of care is easily established. 2. Centralized services. 3. Allows for more day-to-day planning and resource allocation. 4. Autonomy around concise and consistent referral criteria. 5. Hub for education and research in PC. 	<ol style="list-style-type: none"> 1. Startup costs, overhead, and budgetary implications to be considered to launch these clinics. 2. Need for additional support staff in the clinic. 3. Scheduling challenges may be unforeseen because of the high volume of patients but limited providers in these PC clinics.
2. Embedded PC clinics	PC providers co-located within specialty care (e.g., oncology care model)	<ol style="list-style-type: none"> 1. Immediate access to PC within routine care. 2. Facilitates collaboration between PC and specialty providers. 3. Facilitates destigmatization of PC referral among providers and patients. 4. Cost effective for initial integration of PC within hepatology because of shared space, support staff, and other clinical resources. 	<ol style="list-style-type: none"> 1. Consultation may be hastened because of space and volume issues, as the needs of individual patients usually drive the PC consultation. 2. Patients may be rushed because of perception of spending too much time in the clinic and may not be prepared to spend additional time. 3. Financing may require more administrative support.
3. Inpatient PC consultation	PC team consulted during hospitalization	<ol style="list-style-type: none"> 1. Identifies high-need population. 2. Helps reduce health care use and develop end-of-life care goals. 	<ol style="list-style-type: none"> 1. Limited continuity of care. 2. Usually, it is too late for the patients to receive the plethora of benefits of PC. 3. Limited number of PC providers available for high needs of inpatients.
4. Dedicated inpatient PC units	PC team housed on one unit dedicated to deliver PC in conjunction with curative/ongoing care	<ol style="list-style-type: none"> 1. A dedicated inpatient unit can help bring together resources needed to deliver the best PC. 2. Cost savings for the institution, as this can help reduce readmissions and health care use. 	<ol style="list-style-type: none"> 1. Planning and investment to design such a unit by the hospital administrators requires PC administrative expertise. 2. Ongoing challenges to maintain throughput, given the unit will care for a seriously ill population.
5. Telehealth-based PC	Use of remote technology to deliver PC	<ol style="list-style-type: none"> 1. PC providers can deliver care to patients irrespective of the distance or patients' willingness to return to clinics for additional appointments. 2. Video conferencing provides a glimpse into the homes and social contexts of patients, making PC more informed. 	<ol style="list-style-type: none"> 1. Reimbursement is challenging and varies across states. 2. Relies on technology and is limited to those with access to the Internet.
6. Home-based PC	PC providers conduct home visits and deliver PC at patient's home	<ol style="list-style-type: none"> 1. Comfort at home is maintained while PC continues. 2. Increased satisfaction with care. 3. Reduced hospitalizations and ED visits. 4. More at-home deaths. 	Limited availability and coverage.

Abbreviations: ED, emergency department; M.D., medical doctor; N.P., nurse practitioner; PC, palliative care; R.N., registered nurse.

evidence-based PC to their patients with supportive care needs (e.g., ACP, goals-of-care communication, symptom management) in addition to offering all appropriate advanced therapies for patients with ESLD as routine practice. This hypothesis is being tested in the PAL-LIVER study.⁽¹⁶⁾

SCREENING TOOLS TO AID PC INTERVENTION AT AN EARLY STAGE OF ESLD

It is important to identify patients with ESLD who may benefit from nonhospice PC early in their disease trajectory. Screening tools have been developed and validated to help identify patients for whom PC can be triggered in other settings, such as emergency departments. However, few tools exist to identify unmet needs among patients with ESLD. One such tool for inpatients with ESLD at high risk of dying within 1 year includes five criteria: (1) Child-Pugh class C, (2) more than one liver-related admission within the previous 6 months, (3) ongoing alcohol use in the context of known alcohol-associated liver disease, (4) unsuitability for LT, and (5) World Health Organization (WHO) performance score of 3 or 4 (a cumulative score > 3 can be used to trigger PC referral).⁽²²⁾ Other more general screening tools can be applied to patients with ESLD, such as emergency-department PC, which includes three simple criteria: (1) presence of a life-limiting illness, (2) unmet PC needs (e.g., symptoms, functional decline, frailty, new onset of complications, limited social support), and (3) hospital admissions.⁽³⁶⁾

To intervene at an early stage of illness, it is important to use screening tools as standard practice. However, the feasibility of including these screening tools within hepatology practices needs further evidence to determine. Instruments such as the Edmonton Symptom Assessment Score (ESAS) for symptoms, the Patient Health Questionnaire 9 (PHQ-9) for depression, and the Distress Thermometer (DT) for distress can also be used. The ESAS assesses pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, feeling of well-being, shortness of breath, and others (including disease-specific symptoms such as muscle cramps, itching, sexual function, and sleep). The PHQ-9 includes nine questions assessing depression, with higher scores reflecting a greater severity of depression. The DT is a brief, valid instrument to

assess the severity of psychosocial distress in patients with serious illnesses and helps initiate conversations about a wide range of difficulties, in addition to the services and resources that may help address them.

GOALS-OF-CARE DISCUSSIONS

Effective communication is the key to eliciting patient's personal goals and preferences and aligns those with their care management plans. Research has shown that communications about goals of care lead to improved patient health outcomes and a reduced intensity for end-of-life care acts. These should be conducted at an early stage of illness, such as once a diagnosis of cirrhosis is made, but can change over time and therefore must be revisited. The hepatology team can play a pivotal role in eliciting these goals.⁽³⁷⁾ However, clear evidence on how many of these discussions happen during routine hepatology consultations remains unclear. There are standard educational courses available to learn about goals of care such as VitalTalk and OncoTalk, which have been widely used to improve communication skills among providers.⁽³⁸⁾ These are based on effective communication strategies to elicit and deliver personalized care. These can be a part of faculty development within hepatology. Furthermore, a framework such as the REMAP tool (Reframe, Expect emotion, Map out patient goals, Align with goals, and Propose a plan) can be used by the hepatology team to improve goals-of-care discussions.⁽³⁹⁾

ADVANCE CARE PLANNING

ACP is a mechanism for developing future health care goals, to be inclusive of personal values and preferences. Discussions around ACP provide moments to explain the patient's current health situation in the broader context of the overall trajectory of liver disease, treatment options, and potential outcomes associated with each (disease and treatments). In addition, these discussions ameliorate surrogate decision-makers' anxiety and depression and reduce unwanted care acts toward the end of life. A framework tailored to cirrhosis outlining the best-practice tools for ACP has been published by Brisebois et al.⁽⁴⁰⁾ They outline the key elements of ACP process as (1) elicitation of the patient's perspectives, (2) assessment of readiness to discuss ACP and choose a surrogate person, (3) education of patients (using educational resources

on cirrhosis and its complications), (4) description of the focus of care to be inclusive of curative therapy and symptom management, (5) discussion of prognosis using tools that include comorbidities, (6) review of liver-disease complications, (7) review of available local resources for patients and their families, and (8) documentation of goals of care. For compensated cirrhosis, eliciting patients' health goals is important. As they enter the decompensated phase, in-depth discussions on prognosis, treatment options, and symptoms are warranted. Brisebois and colleagues⁽⁴⁰⁾ recommend that these discussions occur, irrespective of LT eligibility.

CONCURRENT CARE MODELS

In 1990, WHO was the first to propose a concurrent care model in which PC was offered from the time of diagnosis of cancer.⁽⁴¹⁾ This was without evidence until the 2000s, when multiple studies in cancer demonstrated that PC effectively improved patients' QOL, symptoms, and surprisingly, survival.⁽⁷⁾ Similarly, although PC and LT are often viewed as mutually exclusive, a concurrent care model may prove beneficial.⁽⁴²⁾ Especially for patients with ESLD who hope to undergo transplantation but risk organ rejection, infection, and posttransplant morbidity in the setting of an already diminished QOL before transplantation, PC can optimize care. A quality improvement study in a Veterans Affairs setting, designed to proactively identify patients with a Model for ESLD (MELD) score ≥ 14 and/or hepatocellular carcinoma (HCC); patients were referred for a PC consultation through a care coordinator.⁽⁴³⁾ The results showed that PC consultations improved the likelihood of being considered for LT and the likelihood of completing the transplantation evaluations. Telehealth could potentially be used to integrate PC within LT care, as has shown to work within liver practices.⁽⁴⁴⁾

Another prospective study conducted in a surgical intensive care unit (SICU) for patients undergoing LT tested a two-part intervention of interdisciplinary communication between providers and patients/families: family support, goals-of-care discussion, and prognosis at admission and a follow-up interdisciplinary family meeting 72 hours later.⁽⁴⁵⁾ The intervention increased goals-of-care discussions (2%-38%), increased do-not-resuscitate status (52%-81%),

and decreased SICU length of stay without affecting mortality. The authors concluded that concurrent PC can be delivered in a SICU setting and can potentially improve end-of-life care. However, there is a high need to educate LT providers on PC benefits for patients and their caregivers.

CAREGIVER SUPPORT

Caregivers of patients with ESLD have high rates of undiagnosed clinical depression, and a higher burden is observed among those who care for patients with frequent hospitalizations, hepatic encephalopathy, or active alcohol use.⁽⁴⁶⁾ Bajaj and colleagues⁽⁴⁷⁾ reported an increased caregiver burden, especially for those caring for patients whose liver-disease severity was high. This increased burden, in general, has been linked to increased mortality in addition to depression and anxiety. Research shows that caregivers who received PC were less likely to have depression or grief.⁽⁴⁸⁾ Through nonhospice PC, caregivers can be evaluated for their burden and distress and linked to additional supportive resources. This may prove to be beneficial for both caregivers and their patients.

Key Steps to Integrate Nonhospice PC Into ESLD Care

Based on the above-described structures and processes, and the current situation of nonhospice PC, there are five things that can be applied to improve PC integration within the treatment of ESLD:

1. Provider education on nonhospice PC, as brief courses or as an integral part of their fellowship training;
2. Universal use of prognostic tools and screening of symptoms, depression, and distress within routine care, coupled with predetermined alerts to promote PC service;
3. Development of clear criteria for PC referrals, such as MELD score, occurrence of an acute-decompensation event, development of HCC beyond an early stage, number of hospitalizations, and presence of comorbidities;

4. Inclusion of goals-of-care and ACP discussions as a part of routine ESLD care, including at the time of transplantation evaluation, at the time of wait-listing or delisting, or when no other curative options exist; and
5. Identification of methods to assess and address caregiver burden, QOL, and distress separately from patients, coupled with referrals made on the basis of the evaluations.

Palliative Care for Liver Diseases Study (Introducing PC Within the Treatment of ESLD)

The Patient-Centered Outcomes Research Institute (PCORI) has invested in large-scale comparative-effectiveness trials testing PC models and ACP approaches. One of these is targeting the population with ESLD. The Palliative Care for Liver Diseases (PAL LIVER) study aims to compare a consultative PC model with trained hepatologist-led PC delivery. It is a multicenter cluster-randomized study, with clinical centers as the units of randomization.⁽¹⁶⁾ The primary hypothesis is that the trained hepatologist-led PC model will have better improvement in QOL (from baseline to 3 months) than the consultative model. Delivering PC in the context of routine hepatology care will build on an established relationship between the patient and his/her hepatologist. Furthermore, it will be more pertinent, given the hepatologist's understanding of the disease process that includes the prognosis and ramifications of each complication.

A PC training program tailored to liver diseases has been developed to formally train hepatology providers in model 2. The study is currently enrolling (ClinicalTrials.gov identifier NCT03540771) and is recruiting dyads (i.e., patients and caregivers together). The intervention is tailored toward both patients and caregivers and uses a PC checklist for all study visits. The visits are being billed to insurance, given the pragmatic nature and an aim to inform real-world practice. This study has brought the two specialties of PC and hepatology together, to partner

and improve the care of patients with ESLD and their caregivers. Through this collaboration, the study has been able to implement both models in distinct settings. The results are projected to improve understanding of optimal integration of PC into the clinical workflow. However, conducting PC research has its own inbuilt challenges. Some ongoing challenges to recruitment include health-related patient factors (such as uncertain prognosis/complications, physical and mental challenges, patient not too sick, or does not understand the value of PC) and social barriers (fear, resistance, additional time and travel); caregiver factors such as mistrust, limited information, beliefs, fear of intrusion, and false hopes; and provider factors such as time sensitivity, workload, and other competing priorities.

Conclusions

Nonhospice PC is underused in ESLD care, despite a great need and potential to improve patient and family-member QOL and reduce costs. Significant barriers exist, with an unclear understanding of how to integrate PC within the treatment of ESLD. The structures and processes described in this review can guide the development of programs and interventions to improve nonhospice PC integration within ESLD care. The provision of training on PC for hepatology trainees and established practitioners will facilitate the implementation of this important integration. The ongoing PAL LIVER study aims to prove that early integration of PC in the care of ESLD can lead to an improvement in patients' QOL and demystify some of the key challenges to support PC integration.

Future collaborative research needs to continue between nonhospice PC and hepatology to test effective PC education approaches for hepatologists: delineating clinical criteria that can trigger PC services for patients with ESLD, advanced-practice providers delivering PC within hepatology offices to accommodate the busy schedules of hepatologists and patients' limited time with hepatologists, or using telehealth-based PC approaches. Furthermore, it will be important to identify which subgroups with ESLD benefit the most from PC, how much PC can be delivered by hepatologists, and the optimal methods of conducting routine assessments of symptoms,

depression, and distress within routine hepatology practice. Finally and critically, it is important to understand the financing of additional PC services within hepatology practices, supporting value-based medicine as opposed to a fee-for-service approach.

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REFERENCES

- Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. *Gastroenterology* 2013;145:375-382.e1-2.
- U.S. Department of Health and Human Services; Centers for Disease Control; National Center for Health Statistics. Health, United States, 2017, With Special Feature on Mortality. National Center for Health Statistics, 2018. Accessed December 4, 2019. <https://www.cdc.gov/nchs/data/health/us17.pdf>
- Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: observational study. *BMJ* 2018;362:k2817.
- Peng JK, Hepgul N, Higginson IJ, Gao W. Symptom prevalence and quality of life of patients with end-stage liver disease: a systematic review and meta-analysis. *Palliat Med* 2019;33:24-36.
- Verma M, Horrow J, McManus K, Navarro V. Exploring the burden, unmet needs and quality of life of caregivers of patients being evaluated for liver transplant. *HEPATOLOGY* 2019;70(Suppl.):446A.
- Beasley A, Bakitas MA, Edwards R, Kavalieratos D. Models of non-hospice palliative care: a review. *Ann Palliat Med* 2018;8(Suppl. 1):S15-S21.
- Kavalieratos D, Corbelli J, Zhang D, Dionne-Odom JN, Ernecoff NC, Hanmer J, et al. Association between palliative care and patient and caregiver outcomes: a systematic review and meta-analysis. *JAMA* 2016;316:2104-2114.
- Lanken PN, Terry PB, DeLisser HM, Fahy BF, Hansen-Flaschen J, Heffner JE, et al.; ATS End-of-Life Care Task Force. An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med* 2008;177:912-927.
- Verma M, Navarro V. Palliative care for end-stage liver disease population. *J Palliat Med* 2017;20:4.
- Jordan RI, Tandon P. Emerging role of palliative care in patients with advanced liver disease. *Semin Liver Dis* 2019; <https://doi.org/10.1055/s-0039-3400259>.
- Rush B, Walley KR, Celi LA, Rajoriya N, Brahmia M. Palliative care access for hospitalized patients with end-stage liver disease across the United States. *HEPATOLOGY* 2017;66:1585-1591.
- Barnes A, Woodman RJ, Kleinig P, Briffa M, To T, Wigg AJ. Early palliative care referral in patients with end stage liver disease is associated with reduced resource utilisation. *J Gastroenterol Hepatol* 2019; <https://doi.org/10.1111/jgh.14877>.
- Kathalia P, Smith A, Lai JC. Underutilization of palliative care services in the liver transplant population. *World J Transplant* 2016;6:594-598.
- Dunn SH, Rogal SS, Maier MM, Chartier M, Morgan TR, Beste LA. Access to comprehensive services for advanced liver disease in the Veterans Health Administration. *Dig Dis Sci* 2019;64:3471-3479.
- Sprange A, Ismond KP, Hjartarson E, Chavda S, Carbonneau M, Kowalczewski J, et al. Advance care planning preferences and readiness in cirrhosis: a prospective assessment of patient perceptions and knowledge. *J Palliat Med* 2019; <https://doi.org/10.1089/jpm.2019.0244>.
- Verma M, Kosinski AS, Volk ML, Taddei T, Ramchandran K, Bakitas M, et al. Introducing palliative care within the treatment of end-stage liver disease: the study protocol of a cluster randomized controlled trial. *J Palliat Med* 2019;22(Suppl. 1):S34-S43.
- Shinall MC Jr, Karlekar M, Martin S, Gatto CL, Misra S, Chung CY, et al. COMPASS: a pilot trial of an early palliative care intervention for patients with end-stage liver disease. *J Pain Symptom Manage* 2019;58:614-622.e3.
- Chung R; Massachusetts General Hospital. A randomized controlled trial of an advanced care planning video decision support tool for patients with end-stage liver disease. <https://clinicaltrials.gov/ct2/show/NCT03557086>. Updated October 4, 2019. Accessed Jan 3, 2020.
- Wray CJ; University of Texas Health Science Center, Houston. Early symptom control and palliative care referral for advanced hepatocellular carcinoma; a randomized control trial. <https://clinicaltrials.gov/ct2/show/NCT02556619>. Updated April 22, 2019. Accessed Jan 3, 2020.
- Kimbell B, Murray SA, Byrne H, Baird A, Hayes PC, MacGilchrist A, et al. Palliative care for people with advanced liver disease: a feasibility trial of a supportive care liver nurse specialist. *Palliat Med* 2018;35:919-929.
- Hansen L, Lyons KS, Dieckmann NF, Chang MF, Hiatt S, Solanki E, et al. Background and design of the symptom burden in end-stage liver disease patient-caregiver dyad study. *Res Nurs Health* 2017;40:398-413.
- Hudson BE, Ameneshoa K, Gopfert A, Goddard R, Forbes K, Verne J, et al. Integration of palliative and supportive care in the management of advanced liver disease: development and evaluation of a prognostic screening tool and supportive care intervention. *Frontline Gastroenterol* 2017;8:45-52.
- Carbonneau M, Davyduke T, Spiers J, Brisebois A, Ismond K, Tandon P. Patient views on advance care planning in cirrhosis: a qualitative analysis. *Can J Gastroenterol Hepatol* 2018;40:40518.
- Ufere NN, Donlan J, Waldman L, Patel A, Dienstag JL, Friedman LS, et al. Physicians' perspectives on palliative care for patients with end-stage liver disease: a national survey study. *Liver Transpl* 2019;25:859-869.
- Aldridge MD, Hasselaar J, Garralda E, van der Eerden M, Stevenson D, McKendrick K, et al. Education, implementation, and policy barriers to greater integration of palliative care: a literature review. *Palliat Med* 2016;30:224-239.
- Beasley AM, Bakitas MA, Ivankova N, Shirey MR. Evolution and conceptual foundations of nonhospice palliative care. *West J Nurs Res* 2019;41:1347-1369.
- Epstein RM, Street RL Jr. The values and value of patient-centered care. *Ann Fam Med* 2011;9:100-103.
- Bakitas M, Dionne-Odom JN, Pamboukian SV, Tallaj J, Kvale E, Swetz KM, et al. Engaging patients and families to create a feasible clinical trial integrating palliative and heart failure care: results of the ENABLE CHF-PC pilot clinical trial. *BMC Palliat Care* 2017;16:45.

- 29) Hui D, Hannon BL, Zimmermann C, Bruera E. Improving patient and caregiver outcomes in oncology: team-based, timely, and targeted palliative care. *CA Cancer J Clin* 2018;68:356-376.
- 30) Luckett T, Phillips J, Agar M, Viridun C, Green A, Davidson PM. Elements of effective palliative care models: a rapid review. *BMC Health Serv Res* 2014;14:136.
- 31) Quill TE, Abernethy AP. Generalist plus specialist palliative care—creating a more sustainable model. *N Engl J Med* 2013;368:1173-1175.
- 32) Wiener L, Weaver MS, Bell CJ, Sansom-Daly UM. Threading the loak: palliative care education for care providers of adolescents and young adults with cancer. *Clin Oncol Adolesc Young Adults* 2015;5:1-18.
- 33) Wittenberg-Lyles E, Goldsmith J, Ferrell B, Burchett M. Assessment of an interprofessional online curriculum for palliative care communication training. *J Palliat Med* 2014;17:400-406.
- 34) Pelayo-Alvarez M, Perez-Hoyos S, Agra-Varela Y. Clinical effectiveness of online training in palliative care of primary care physicians. *J Palliat Med* 2013;16:1188-1196.
- 35) Amro OW, Ramasamy M, Strom JA, Weiner DE, Jaber BL. Nephrologist-facilitated advance care planning for hemodialysis patients: a quality improvement project. *Am J Kidney Dis* 2016;68:103-109.
- 36) George N, Barrett N, McPeake L, Goett R, Anderson K, Baird J. Content validation of a novel screening tool to identify emergency department patients with significant palliative care needs. *Acad Emerg Med* 2015;22:823-837.
- 37) Kelly SG, Rice JP. Palliative care for patients with end-stage liver disease: the role of the liver team. *Clin Liv Dis (Hoboken)* 2015;6:22-23.
- 38) Arnold RM, Back AL, Baile WF, Edwards KA, Tulsy JA. The OncoTalk/VitalTalk model. In: Kissane DW, Bultz BD, Butow PN, Bylund CL, Noble S, Wilkinson S, eds. *Oxford Textbook of Communication in Oncology and Palliative Care*. Oxford: Oxford University Press; 2017:363-369.
- 39) Childers JW, Back AL, Tulsy JA, Arnold RM. REMAP: a framework for goals of care conversations. *J Oncol Pract* 2017;13:e844-e850.
- 40) Brisebois A, Ismond KP, Carbonneau M, Kowalczewski J, Tandon P. Advance care planning (ACP) for specialists managing cirrhosis: a focus on patient-centered care. *HEPATOLOGY* 2018;67:2025-2040.
- 41) World Health Organization. Cancer pain relief and palliative care. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1990;804:1-75.
- 42) Wentlandt K, Weiss A, O'Connor E, Kaya E. Palliative and end of life care in solid organ transplantation. *Am J Transplant* 2017;17:3008-3019.
- 43) Walling AM, Schreiber-Baum H, Pimstone N, Asch SM, Robinson L, Korlekar S, et al. Proactive case finding to improve concurrently curative and palliative care in patients with end-stage liver disease. *J Palliat Med* 2015;18:378-381.
- 44) Konjeti VR, Heuman D, Bajaj JS, et al. Telehealth-based evaluation identifies patients who are not candidates for liver transplantation. *Clinical Gastroenterol Hepatol*, 2019;17:207-209.
- 45) Lamba S, Murphy P, McVicker S, Smith JH, Mosenthal AC. Changing end-of-life care practice for liver transplant service patients: structured palliative care intervention in the surgical intensive care unit. *J Pain Symptom Manage* 2012;44:508-519.
- 46) Nguyen DL, Chao D, Ma G, Morgan T. Quality of life and factors predictive of burden among primary caregivers of chronic liver disease patients. *Ann Gastroenterol* 2015;28:124-129.
- 47) Bajaj JS, Wade JB, Gibson DP, Heuman DM, Thacker LR, Sterling RK, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *Am J Gastroenterol* 2011;106:1646-1653.
- 48) Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008;300:1665-1673.
- 49) Center to Advance Palliative Care. About Palliative Care. <https://www.capc.org/about/palliative-care/>. Accessed January 3, 2020.
- 50) Ferrell R, Twaddle ML, Melnick A, Meier DE. National consensus project clinical practice guidelines for quality palliative care guidelines. *J Palliat Med* 2018;21:1684-1689.
- 51) Baumann AJ, Wheeler DS, James M, Turner R, Siegel A, Navarro VJ. Benefit of early palliative care intervention in end-stage liver disease patients awaiting liver transplantation. *J Pain Symptom Manag* 2015;50:882-886.