

EASL position paper on palliative care in advanced chronic liver disease

Sumita Verma^{1,2,*}, Matthias Pinter³, Lucia Macken^{1,2}, Patrizia Künzler-Heule^{4,5}, Lise Lotte Gluud⁶, Bart Takkenberg⁷, Rui Nunes⁸, Liana Gheorghe^{9,10,11}, Wendy Prentice^{12,13}, Ben Hudson¹⁴

Summary

Deaths from advanced chronic liver disease have increased significantly across Europe, with most affected patients not receiving a liver transplant. Despite this increasing burden, inequities in the provision of palliative care persist. Many patients are referred to specialist palliative care only in the final days or weeks of life and may continue to undergo futile invasive procedures. Drawing on the best available evidence, this position paper offers guidance to clinicians on the provision of palliative care to patients with advanced chronic liver disease, with the aim of improving the quality of life of this vulnerable cohort.

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Introduction

In the last 50 years, deaths from liver disease have quadrupled in Europe,^{1–3} with liver disease now being the second leading cause of years of working life lost.⁴ The 2022 European Association for the Study of the Liver (EASL) - Lancet Liver Commission called for early diagnosis and management of treatable liver diseases.⁴ Most patients with advanced chronic liver disease (ACLD) will not receive a liver transplant.^{5,6} In addition, ACLD is characterised by an uncertain trajectory, a complex symptom burden, distress, and high caregiver workload and healthcare utilisation. Despite this, the provision of timely palliative care (PC) in ACLD remains a clear unmet need. Recent calls to improve PC in ACLD have been endorsed by the Lancet Liver Commission and other Hepatology societies.^{4,7–9}

This EASL position paper addresses the role of PC in the management of patients with ACLD and provides guidance to all healthcare professionals (HCPs) caring for this cohort.

Methods

Ten experts contributed to this position paper – seven hepatologists, one specialised advanced practice nurse, one PC physician with expertise in ACLD symptom management and PC, and one bioethicist. The following steps were adopted in developing this position paper.

- The panel met to identify key areas requiring attention and discussion.

- Once the topic areas were identified, the panel formulated relevant clinical questions. As this is not a clinical practice guideline, the PICO format for questions and the Delphi panel process were not adopted.
- Relevant question(s) were allocated to each panel member.
- Seven clinically relevant topics were identified, and for each, a summary statement and recommendations are included. The recommendations are based on the current best available evidence as assessed by the 10 experts. Due to the paucity of randomised controlled trials (RCTs) in this topic area, the quality and strength of evidence are not stated. Clinicians need to be cognisant of this fact when considering the recommendations.

Introduction to palliative care

What are current concepts in PC and why is it relevant to ACLD?

The modern hospice movement has its origins in the work of Dr Cicely Saunders in the 1960s and has since evolved from a philosophy of care to a professional discipline with expertise in symptom management, psychosocial and spiritual care, communication, decision making, caregiver support, and end-of-life care (EoLC).¹⁰ Over time, there have been many debates about definitions and the resulting service standards and expectations.

The World Health Organization (WHO) first defined PC in 1989 as care for those whose disease is no longer curable. The

* Corresponding author. Address: Brighton and Sussex Liver Research Centre, Department of Clinical and Experimental Medicine, Brighton & Sussex Medical School, Main Teaching Building Room 2.17, University of Brighton and University of Sussex, Brighton, UK. E-mail address: s.verma@bsms.ac.uk
<https://doi.org/10.1016/j.jhepr.2025.101686>



latest updated WHO definition from 2020 is “Palliative Care is an approach that improves the quality of life of patients (adults and children), and their families who are facing problems associated with life-threatening illness”.¹¹ PC prevents and relieves suffering through early identification, correct assessment, and treatment of pain and other problems, whether physical, psychosocial or spiritual, and remains true to the original tenet.¹² This definition is particularly relevant for patients with ACLD, who often experience complex symptoms such as fatigue, large volume ascites and hepatic encephalopathy (HE), along with emotional and spiritual distress. PC provides a holistic approach that supports both patients with ACLD and their caregivers, addressing the condition’s unpredictable trajectory and the significant caregiver burden.

There is considerable international variability in the development and delivery of PC services, which depends on available resources and health-policy priorities. European consensus has led to a high level of agreement regarding definitions of palliative and hospice care, favouring the terms ‘specialist palliative care’ and ‘generalist palliative care’, as opposed to ‘non-specialist palliative care’ (Table 1).^{13,14} Outside the US, the term supportive care has not been widely recognised as a synonym for PC.¹⁵ This conceptual model from the US places PC under the umbrella of supportive care (or supportive oncology), a broader term that includes other supportive fields/disciplines.¹⁶

Patients with ACLD have a reduced life expectancy, significant physical and psychosocial issues, and poor health-related quality of life (HRQoL). To effectively address the needs of this patient group, and their caregivers, holistic assessment skills, clear communication and appropriate medical, psychosocial and practical support are needed from those who are delivering treatment and care. All HCPs, including those involved in managing patients with ACLD, have a responsibility to provide generalist PC with support from specialist PC services in complex cases. PC should be viewed as a means of optimising HRQoL for patients and caregivers, which can be provided in parallel with active/curative management of ACLD, including liver transplantation.¹⁷ PC is not synonymous with EoLC.¹⁷

A key principle in supporting patients with ACLD is to enable early, open and honest conversations with professionals whom they trust and have an ongoing therapeutic relationship,¹⁸ particularly as development of HE (which can have an unpredictable course), may impact upon decision making ability in the

future. Attention to detail is essential in all aspects of care, empowering patients and caregivers to manage physical and psychological symptoms proactively. Well-coordinated care (e.g. between primary and secondary care, and across hospital departments) has been shown to impact positively on patient outcomes and healthcare resource utilisation.¹⁷

What are the benefits of PC in advanced non-cancer chronic conditions, including ACLD?

PC is increasingly recognised as an essential component of patient care, extending beyond oncology to encompass serious non-malignant diseases, such as chronic lung, heart, and kidney disease. In these disease areas, practice guidelines and recommendations already incorporate PC as a fundamental component of management (Table S1). Key themes include the early integration of PC, the need for multidisciplinary teams (MDTs) to undertake holistic assessments, symptom management, support for caregivers, and the importance of advance care planning (ACP). Implementing these strategies can significantly enhance patient HRQoL and optimise healthcare resource utilisation.^{19–22}

Several RCTs have evaluated the impact of PC interventions on patients with incurable diseases and support these guidelines (Table S2). In advanced heart failure, interdisciplinary palliative interventions comprising goals-of-care discussions, symptom management and mental health support have led to significant improvements in HRQoL, depression, anxiety, spiritual well-being, improvements in pain intensity and improved documentation of ACP.^{23–26} For patients undergoing haematopoietic stem cell transplantation, integrating inpatient PC focusing on physical and psychological symptom management was associated with a smaller decline in HRQoL and better HRQoL, with lower depression levels compared to standard care.²⁷

These studies highlight the critical role of PC in the management of advanced, potentially life-limiting diseases. These principles are also highly relevant to non-malignant conditions such as ACLD, given the parallels in disease trajectory and patient needs. However, irrespective of disease aetiology, PC delivery needs to be adapted to the needs of individual patients. Studies in incurable cancer suggest that, dependent on the type of malignancy, there is heterogeneity in how and when patients benefit from PC.²⁸

Table 1. Modern concepts in palliative care.

Concept	
Palliative care	A holistic approach to care for patients with serious illness, addressing physical, psychosocial, and spiritual needs focusing on improved quality of life. It includes but is not synonymous with end-of-life-care. Palliative care supports patients and caregivers and can be provided alongside active management of chronic liver disease.
Supportive care	Has been used interchangeably with palliative care but is not universally accepted as a synonym for palliative care.
End-of-life care	Care provided in the final phase of life, typically the last weeks or days, focusing on comfort and dignity as death approaches. However, there remains variation in relation to time frames associated with the term end-of-life-care – some consider this to be those in the last year of their life, whereas others focus more on the final phase of life. This can lead to confusion.
Advance care planning	A process of discussing and documenting a person’s preferences for future medical care, including values, goals, and preferred place of care, or death.
Generalist palliative care	Basic palliative care provided by non-specialist healthcare professionals (e.g. hepatologists, general practitioners, nurses) as part of routine clinical care.
Specialist palliative care	Care delivered by professionals with advanced training in palliative medicine, used for complex symptom management, ethical dilemmas, and intensive psychosocial support.
Multidisciplinary team	A collaborative group of healthcare providers (e.g. physicians, nurses, social workers, and psychologists) working together to deliver coordinated, patient-centred palliative care.

Summary statement

PC is not limited to oncology and has become essential in other non-cancer chronic conditions. It is a holistic approach for patients and families dealing with life-threatening and life-limiting conditions. RCTs have confirmed improvements in HRQoL, symptom control, mental health, psychological and spiritual support, and opportunities for ACP. These general principles are also highly relevant in ACLD, where symptoms are complex and disease trajectory unpredictable. There is increasing consensus on the structure and terminology of generalist and specialist PC, with a focus on multidisciplinary approach and early integration of services. PC includes but is not synonymous with EoLC.

Recommendations

- HCPs managing ACLD should look to align principles of PC adopted in other life-limiting, non-malignant conditions, with emphasis on the holistic assessment of patient and caregiver needs, and on improving HRQoL. Optimal timing may differ depending on individual needs/preferences.
- PC can be more effective when introduced at an earlier stage in the disease trajectory and should be considered in parallel to ongoing curative treatments. PC is not synonymous with EoLC.
- HCPs involved in care of patients with ACLD should be educated and trained to deliver generalist PC including discussions around ACP.
- PC should be delivered in a multidisciplinary setting, with defined team roles, referral processes, and standards for shared decision making.

Symptom burden and HRQoL

What is the symptom burden experienced by patients with ACLD and how does this impact HRQoL?

Although ACLD complications including ascites, HE, and variceal bleeding are well recognised,²⁹ the symptom burden experienced by those with ACLD is less well described.

Patients with ACLD experience complex physical and psychosocial challenges. Owing to a combination of younger age, stigmatisation, and higher rates of social disadvantage and deprivation, these challenges are often reported at a greater severity than in other chronic diseases.^{4,30,31} Patient-reported symptoms in ACLD are not well assessed in routine clinical practice,¹⁷ despite being independently associated with attendance at emergency departments.^{32,33} A recent systematic review highlighted the following prevalence of symptoms in patients with ACLD: pain (30%–79%), breathlessness (20%–88%), muscle cramps (56%–68%), sleep disturbance (insomnia 26%–77%, daytime sleepiness 29.5%–71%), psychological symptoms (depression 4.5%–64%, anxiety 14%–45%), and erectile dysfunction (53%–93%).³⁴

Physical symptoms

Pain. The physical symptom most frequently and consistently reported is pain, the burden of which is comparable to that

reported for patients with lung and colon cancer.^{34–36} A nationally representative sample from the US found that in liver disease, pain was the most distressing and severe symptom reported,³⁵ with functional limitations similar to, or greater than those in other painful chronic conditions.³⁶ In hospitalised patients with ACLD undergoing consideration for transplantation, pain was reported in up to 77%.³⁷

Fatigue. Although well described in the context of cholestatic liver diseases,^{38,39} fatigue and lack of energy are also commonly reported in those with ACLD from other aetiologies.^{35,40–42} Fatigue is linked to higher levels of depression and is both more frequent and more severe in advanced disease.^{30,43} Lack of energy is often graded as a severe and distressing symptom that can be associated with sleep disturbances and HE.^{35,43} When evaluating patients with fatigue, other contributory factors should be taken into account, including anaemia and the impact of medications.^{44,45}

Sleep-wake disturbance. Sleep disturbances include insomnia, daytime sleepiness, trouble initiating sleep, and wakefulness.^{34,35,41,46–48} In ACLD, this can be linked to the development of HE, but is also found in those without evidence of neuropsychiatric impairment.⁴⁵ The prevalence of disturbed sleep among those with ACLD has been shown to be as high as 81%.⁴⁸ Contributory factors include muscle cramps,^{34,43,49} restless leg syndrome and pruritus.^{34,45,48} Psychoactive substances, including medication, are also associated with sleep disturbances.^{48,50}

Pruritus. In primary biliary cholangitis, sleep disturbances are well recognised and linked to the severity of pruritus.⁴⁵ Pruritus is reported in up to 64% of the wider population with ACLD.^{34,41,43}

Breathlessness. Breathlessness can affect up to 88% of patients with ACLD,^{34,51} and is multifactorial in nature, being associated with ascites volume, oedema, liver-related cardiac dysfunction, and anaemia.²⁹

Sexual dysfunction. Reduced interest in sex and sexual dysfunction are commonly reported in ACLD, though they are often overlooked in international guidelines.^{29,30,35,43} Sexual dysfunction can often be linked to hormonal changes and hypogonadism.⁵² In men with ACLD, the prevalence of erectile dysfunction can be as high as 93%. Infertility, loss of sexual drive, and testicular atrophy are also frequently reported.^{34,52} In women, anovulation is common, resulting in oligo or amenorrhea, with sexual dysfunction reported in up to 78%.^{34,52} In patients with ACLD, there is a progressive reduction in sexual function with advancing liver disease.⁵² Co-existing factors can negatively affect sexual function, including active alcohol and recreational drug use, pharmacotherapy (e.g. carvedilol), and large volume ascites.⁵²

Frailty and falls. Although frailty is more often associated with older adults, it can affect patients with ACLD across their lifespan and is gaining increasing recognition. It is multidimensional and may not be fully appreciated or assessed during routine clinical care.^{53–55} Frailty is associated with self-reported symptom burden, though studies have not always shown a consistent correlation between liver disease severity and frailty.^{53,56,57} It can also be a surrogate marker for sarcopenia. When present, frailty impacts negatively on activities of daily living, is associated with falls, poor HRQoL outcomes, and predicts higher mortality.^{46,53–55} Although falls are often linked to cognitive dysfunction and HE,^{55,58} they can occur in the absence of HE, and are independently associated with increased mortality.⁵⁹

Muscle cramps. The occurrence of muscle cramps in ACLD is well recognised, though their pathophysiology and management remain unclear.^{43,48,60} Where recorded, muscle cramps are reported in up to 68% of patients with ACLD.³⁴ Cramps are regarded as one of the more distressing physical symptoms, being independently associated with reduced HRQoL.^{40,43,61} The pathophysiology may be linked to a reduction in effective circulating volume in ACLD;⁶² however, a direct association with disease severity or serum electrolyte disturbances has not been demonstrated.^{61,62} Similarly, a direct association between diuretic use and the occurrence of muscle cramps has not been conclusively proven, though diuretics may increase the frequency of symptoms amongst patients with muscle cramps.^{29,61,63,64}

Psychological symptoms

Depression and anxiety. Psychological distress is common in ACLD, being related to severity of the underlying liver disease,⁴³ and associated with an impaired HRQoL.^{46,65} More than half of the ACLD cohort (up to 72% with alcohol-related liver disease [ALD]) report depression, with up to 40% rating symptoms as moderate to severe.^{41,49,51} Depression has also been linked to stigmatisation and lack of social support.⁶⁶ Stigma in patients with ACLD is attributable to multiple factors, including disease aetiology and physical appearance.^{67,68} The presence of depression amongst those with ACLD impacts on the severity of other symptoms, and is associated with poorer outcomes.^{30,49,69} Rates of anxiety are higher in more advanced stages of liver disease, especially in women.⁵⁵ Limited disease information and understanding have been associated with increased anxiety levels.⁶⁶

HRQoL

The presence of ACLD is a predictor of impaired HRQoL,^{66,70} even after adjustment for sociodemographic factors and other comorbidities.⁷¹ HRQoL worsens with advancing severity of liver disease.^{55,70,72} While many physical and psychological factors impact on poorer HRQoL in ACLD,^{34,43,49,55} the main drivers are HE, ascites, frailty, younger age, muscle cramps, and hypoalbuminaemia.^{33,46,73}

Physician-developed disease severity tools typically overlook symptoms not directly related to liver dysfunction, correlate poorly with HRQoL, and lack patient perspectives of lived experience of ACLD.⁷⁴ A recent systematic review reported that only 45% of studies on ACLD and HRQoL used liver-specific tools.⁴⁶ Generic tools utilised include the SF-36 (short form 36),⁷⁵ the Euro-QoL (EQ-5D-5L)⁷⁶ and the ESAS-r (Edmonton symptom assessment system-revised),^{77,78} though these are not validated in ACLD.

While validated disease-specific tools have been developed in hepatobiliary cancer, primary biliary cholangitis, and viral hepatitis,^{79,80} the same is not true in ACLD. This can present a barrier to the assessment of clinical and outcome measures in palliative hepatology trials in ACLD.^{66,77} Palliative hepatology has previously been defined as “holistic care given to patients with advanced liver disease and their families to improve their QoL over the entirety of their illness trajectory, both to and through transplantation, and at the end of life”.⁸¹

Table 2 summarises the liver-specific tools used to assess HRQoL and symptom burden in ACLD. Work is also under way in the UK to develop a liver-specific symptom tool for ACLD.⁵¹

What are the current unmet needs in symptom management in ACLD?

Current literature aiming to identify unmet needs in patients with ACLD consistently shows significant impairments in HRQoL, irrespective of aetiology.^{39,47,66} Provision of PC for this group of patients is linked to many factors, including organisation of healthcare, experience of stigmatisation and deprivation, and HCPs' experience of providing generalist PC.^{17,31,66,82,83}

Key domains of supportive care needs identified include: 'informational or educational' (disease-related information and education), 'practical' (daily living and financial support), 'physical' (symptom management, including abdominal distention, pruritus and fatigue), 'patient care and support' (patient and caregiver support groups and access to allied HCPs, including pharmacists and dietitians) and 'psychological' (including spiritual needs).^{39,47,66}

Current unmet needs in symptom management include pain, muscle cramps, fatigue, frailty, anxiety, and depression. Management of these symptoms is summarised in **Table 3**. Optimal management of muscle cramps has not been established but includes baclofen, taurine supplementation, human albumin solution, pregabalin, pickle juice, stretching and meditation.^{84,85} The multidimensional nature of frailty represents opportunities for targeted improvements in HRQoL,^{53,55} and integrated assessments, along with nutritional support and physical therapy may improve individualised patient care.^{53,54,59} The diagnosis of depression and anxiety should be in line with established diagnostic criteria. Interventions can include, but are not limited to, pharmacotherapy, patient education and psychological support delivered within multi-professional teams⁶⁵ (**Table 3**).

Management of physical symptoms can lead to polypharmacy. Therefore, judicious use of medications in ACLD is important, as psychoactive substances are associated with sleep dysfunction and increased frequency of falls, while diuretics have been suggested to impact the frequency of muscle cramps.^{8,29,61} Diuretics should be discontinued in the context of severe side effects.^{8,29,61} Non-pharmacological management should also be considered, including psychological support for anxiety, or physiotherapy for falls, frailty, and musculoskeletal pain.⁵⁰ Non-pharmacological management of symptoms is a crucial aspect of good PC, particularly in frail patients with ACLD who are at increased risk of side effects, toxicity and drug-drug interactions.

Early PC interventions have been shown to improve symptom burden and lower the rate of hospital readmission in those with ACLD.^{41,86} PC in cancer is well established and improves HRQoL;⁸⁷ however, in the context of ACLD, PC is still a developing area. Patients with ACLD who are ineligible for liver transplantation seldom receive PC, except in the context of hepatocellular carcinoma (HCC).^{88,89}

In ACLD, PC is typically introduced late in the disease trajectory and patients are often subjected to the futile continuation of aggressive interventions toward EoL.⁹⁰ A systematic

Table 2. Liver-specific quality of life and symptom assessment tools. Adapted from Verma S et al. *J Hepatol.* 2023;79:1236-1253.⁷⁷

Name of tool	Details	Strengths	Limitations	How administered
Short form liver disease quality of life (SF-LDQoL) (last 4 weeks) ²¹⁷	25 item questionnaire. Comprising SF-36 and 36 liver-specific items grouped into nine scales effect of liver disease, memory/concentration, sexual functioning/problem, quality of social interaction, health distress, sleep, loneliness, hopelessness and stigma - Higher scores indicate better HRQoL	- Disease-specific - More responsive/sensitive than CLDQ if advanced cirrhosis - Thorough assessment as combined use of generic/disease-specific tools - Could predict mortality - Available in other languages	Limited use and limited published data	- Paper and pencil, self-administered 20 min to complete
Chronic liver disease questionnaire (CLDQ) ²³¹	29 items, 6 domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function and worry - Higher scores better HRQoL	- Disease-specific - Widely used and easy to use - Simple scoring system - Available in other languages - Most widely used liver-specific tool	- Validated mostly in women, cholestatic liver disease/viral hepatitis, ~70% having no/early cirrhosis (Child-Pugh A) - Lacks sensitivity to detect small variations in HRQoL especially in advanced liver disease (Child-Pugh B/C)	- Self-administered 20 min to complete
Liver disease quality of life (LDQoL) ²³²	12 liver-specific domains: symptoms, effects on activities of daily living, concentration, memory, sexual function, sexual problems, sleep, loneliness, hopelessness, quality of social interaction, health distress and self-perceived stigma of liver disease - Higher scores correspond to better HRQoL	- Maybe more sensitive than CLDQ - Incorporates the SF-36 as well as 12 additional domains including symptoms of liver disease	- Limited published data using English version - Lengthy to complete unless short form used (SF-LDQoL)	- Self-administered 35 min to complete
Liver cirrhosis patient-reported outcome measure (LC PROM) ²³³	- Cirrhosis specific 55 items - Addresses four domains: physical, psychological, social, and therapeutic	Includes treatment satisfaction, compliance and drug side effects	Not in routine use	- Self-administered 10 min to complete
Functional assessment of cancer therapy – hepatobiliary (FACT-Hep) ²³⁴	- Hepatobiliary cancer patients ≥18 years 45-item questionnaire with a 5-point Likert type scale covering five domains (emotional, physical, social and functional well-being) as well as hepatobiliary cancer symptom subscale symptoms - Higher scores indicate better quality of life	- Available in over 40 languages with rigorous translation methodology - Disease-specific (patients with hepatobiliary cancer) - Validated to detect clinical changes - Total and index scores available	- Use only in hepatobiliary cancers - License and potential fee required to obtain translated non-English versions - Cumbersome to score manually (however statistics software algorithms available)	- Self-administered or interview paper and electronic forms 10–15 min to complete
Liver disease symptom index 2.0 (LSDI) ²³⁵	9 symptom severity items: itch, joint pain, abdominal pain, daytime sleepiness, worry about family situation, decreased appetite, depression, fear of complications, jaundice. 9 symptom hinderance items - Higher scores correspond to greater severity of symptoms and impact on daily activities	- Short tool to complete - Focus on symptoms rather than HRQoL	- Limited published data - Only validated in the Netherlands	- Self-administered 10 min to complete
Ascites questionnaire (Ascites-Q) ²¹⁹	11-paired questions assessing the frequency of symptoms using a 6-point scale and their subjective impact on the patient using a 5-point scale - Symptoms covered include fatigue, pain, sleep disturbance and bloating	- Ascites-specific tool - Validated in cirrhosis - Higher convergent validity with QoL visual analogue scale scores	Available in limited number of languages	- Self-administered 5–10 min to complete
Ascites symptoms inventory (ASI-7) ²³⁶	7-item questionnaire with a 5-point scale covering four domains including abdominal bloating and physical restrictions	- Ascites-specific tool - Validated in cirrhosis - Brief and straightforward	- Available in limited number of languages - Focused on symptoms without assessing impact it has on the patient	- Self-administered - Few minutes to complete

HRQoL, health-related quality of life.

review of PC for patients on the transplant waiting list in the US suggested that early PC occurred infrequently; however, when utilised appropriately, it improved symptoms.⁸³ Most patients with ACLD are not suitable for a liver transplant; therefore, the management focus for the majority remains optimisation of symptoms and HRQoL.⁵

Summary statement

Patients with ACLD have complex physical and psychosocial symptomology coupled with a high level of unmet need contributing to poor HRQoL, which worsens with disease severity. Consistently identified areas of unmet need include disease-specific education, practical support with activities of daily living, psychological support, as well as patient and caregiver support. Proactive identification of common symptoms and holistic clinical assessment, including the use of patient-reported outcome tools which assess HRQoL, should be widely integrated into clinical practice. Instigation of PC interventions at an earlier stage in the disease trajectory could improve patient symptoms and HRQoL. Multidisciplinary/interprofessional collaboration enables a holistic approach, allowing for more individualised and coordinated interventions.

Recommendations

- To proactively identify the complex physical and psychological symptoms and unmet needs in ACLD, a multidisciplinary and holistic approach is recommended. Tools to assess HRQoL and symptoms should be integrated into routine clinical care, including the future development of liver-specific tools.
- HCPs should manage potentially modifiable factors resulting in poor HRQoL including HE, psychiatric comorbidities (depression and anxiety), frailty, malnutrition, physical symptoms (pain, muscle cramps and sleep disturbance), anaemia and importantly, address polypharmacy and fall prevention strategies.
- Hepatologists and HCPs should consider instigating early PC in parallel with routine clinical care in patients with ACLD, as the majority of patients will have symptoms regardless of transplant eligibility.

Identifying patients with ACLD who are suitable for PC

What are the benefits of PC in patients with ACLD?

Early integration of PC in hospitalised patients with ACLD improves symptom burden, facilitates ACP, and reduces hospital admissions.^{91,92} A longitudinal early outpatient PC intervention improved physical and psychological symptom burden in liver transplant candidates.⁴¹ Another study found that patients receiving PC integrated within hepatology services had fewer mean hospitalisation days and were more likely to have goals-of-care discussions, complete ACP documentation, and receive hospice involvement compared

with those receiving usual care.⁹³ Integration of a PC physician, specialist liver nurse, and pharmacist into hepatology care is associated with higher uptake of formal ACP, increased outpatient PC referral, a higher likelihood of dying outside of hospital and fewer unplanned hospitalisation days, compared with standard of care.⁹⁴

Two RCTs confirmed the benefits of specialist PC in patients with ACLD and HCC (see also [Palliative research](#) section and [Table 5](#)).^{86,95} Shinall *et al.* randomised patients with ACLD (estimated life expectancy of ≤ 1 year) to usual care, or inpatient specialist PC plus outpatient phone calls by a specialist PC nurse. Despite premature study termination due to slow recruitment, the intervention group had a significantly increased time until first readmission and 4-fold increase in days alive outside the hospital.⁸⁶ In the second RCT, patients with HCC (Barcelona Clinic Liver Cancer [BCLC] stage 0 to C) who received a PC intervention exhibited an improvement in [symptom burden and HRQoL](#), which remained the same or worsened in the control arm.⁹⁵

Besides the impact on symptoms and HRQoL, integrating PC into the management of patients with ACLD reduces healthcare resource utilisation, including fewer invasive procedures, reduced hospitalisations (including intensive care unit bed days), and lower costs.^{92,93,96–98}

What criteria should we use to identify patients with ACLD who need PC?

Determining prognosis in ACLD can be challenging and is therefore often not assessed, or incorrectly assessed, especially if patients are still receiving curative therapies, or are listed for liver transplantation. The benefits of PC interventions are reduced if they are introduced very late in the disease trajectory.^{99,100} Unrealistic expectations from both patient and physician are a common barrier to timely PC in ACLD.¹⁰¹

The UK multicentre EVOLVE study retrospectively reviewed the healthcare utilisation of 803 patients in their last year of life, and assessed factors associated with improved PC provision (measured by documented ACP, PC referral, or discussion around poor prognosis). Patients who had a documented assessment (formal or informal) of transplant suitability, or an objective prognostic score documented were significantly more likely to receive PC.¹⁰² Therefore, by overlooking objective prognostic assessments, opportunities for effective PC can be missed.

Tools that objectively assess prognosis are crucial for the timely identification of patients who are most likely to benefit from PC. Traditional models for assessing prognosis in patients with ACLD are the Child-Turcotte-Pugh (CTP) classification¹⁰³ and the model for end-stage liver disease (MELD) score,¹⁰⁴ along with its derivatives the MELD sodium¹⁰⁵ and MELD 3.0 scores.¹⁰⁶ A CTP ≥ 12 and MELD score ≥ 21 are associated with a median survival of less than 6 months.^{107,108} Whilst well established, these models are designed to predict postoperative and post-interventional mortality and guide liver transplantation; they were not developed to assess the need for PC.

The surprise question (SQ) “Would I be surprised if this person died within the next 12 months” is a simple, experience-based, intuitive screening tool that helps clinicians identify patients with a limited life expectancy who may benefit

Table 3. Symptom management in advanced chronic liver disease – possible management options, following a holistic palliative care assessment.^{9,237}

Symptoms	Associations	Management
Physical		
Pain	Ascites Neuropathic Musculoskeletal	Diuretics, large volume paracentesis, long-term indwelling drains in appropriate context, paracetamol (up to 2 g/day), opiates (hydromorphone, morphine sulphate, oxycodone), avoid non-steroidal anti-inflammatory drugs
Fatigue	Hepatic encephalopathy Poor sleep Mental health Anaemia Endocrine (hypothyroidism/hypo-adrenalism) Pharmacological side effects	Non-pharmacological: education, energy conserving activities, physical and occupational therapy Pharmacological: lactulose, rifaximin, targeted to aetiology Review medications
Sleep-wake disturbance	Hepatic encephalopathy Pruritus Muscle cramps Restless legs Alcohol use disorder Psychoactive substances	Non-pharmacological: sleep hygiene, psychological support, mindfulness Pharmacological: lactulose, rifaximin, melatonin, hydroxyzine Review medications
Pruritus	Cholestatic liver disease Decompensated advanced chronic liver disease	Non-pharmacological: creams, loose fitting clothes Pharmacological: topical; antihistamines, cholestyramine, sertraline
Breathlessness	Ascites Anaemia Fluid overload Portopulmonary and hepatopulmonary syndrome	Diuretics, large volume paracentesis, long-term indwelling drains in appropriate context, benzodiazepines, opiates Targeted management
Sexual dysfunction	Decompensated advanced chronic liver disease Pharmacological side effects Mental Health	Sildenafil and its analogues
Frailty and falls	Hepatic encephalopathy Sarcopenia	Non-pharmacological: allied health professional input including dieticians, physical and occupational therapy Pharmacological: lactulose and rifaximin,
Muscle cramps	Serum electrolytes Diuretics	Non-pharmacological: review diuretics, increasing physical activity Pharmacological: taurine, vitamin E, baclofen, pickle juice
Psychological		
Depression and anxiety	Alcohol and substance use disorder Social isolation Unstable housing Uncertainty in prognosis	Non-pharmacological: addiction services, psychological support and social support/support groups, mental health assessment and support Pharmacological: mirtazapine, citalopram

from PC.¹⁰⁹ The only study in ACLD to evaluate the agreement of the SQ with observed mortality¹¹⁰ showed that when the hepatologist answered "No" to the SQ during hospitalisation (SQ+) patients had a lower 1-year cumulative survival rate than patients where the hepatologist answered "Yes" to the SQ. The sensitivity, specificity, negative and positive predictive values of the SQ for patients with ACLD were 93%, 38%, 92%, and 42%, respectively. Prospective studies are needed to confirm these data.

Another prognostic screening tool for PC intervention in ACLD is the Bristol prognostic score.¹¹¹ The presence of three or more poor prognostic criteria (CTP C disease, ongoing alcohol use, recurrent unplanned admissions, performance status and transplant suitability) predicted 1-year mortality with a sensitivity, specificity and positive predictive value of 72%, 84% and 81%, respectively. Patients screening "positive" were offered a PC intervention which included a consultant-led prognosis discussion, a poor prognosis letter written to the patients' primary care physician, an opportunity for ACP, allocation of a named specialist nurse, and specialist PC review in complex cases. Finally, the SPICT (supportive and palliative care indicators tool) can help HCPs identify individuals with advanced chronic diseases who might benefit from a PC intervention.¹¹²

In conclusion, the presence of decompensated disease, multiple hospital admissions, poor performance status, frailty and ongoing alcohol use, along with judicious use of prognostic tools, could help guide hepatology HCPs in timing the initiation of PC in ACLD (Fig. 1). Because of the paucity of evidence, it is difficult to recommend one tool over another; the best approach is to use them in conjunction alongside individualised clinical assessment.

How best to deliver PC for patients with ACLD when there is prognostic uncertainty?

Patients with ACLD being evaluated or listed for liver transplantation

Patients with ACLD being evaluated or listed for liver transplantation often experience poor HRQoL due to disabling symptoms and significant psychosocial stress related to uncertainty about transplant eligibility and outcomes.¹¹³ Despite this, PC is often not considered, commonly cited barriers being cultural factors, unrealistic patient expectations about their prognosis, and competing demands on clinicians' time.¹⁰¹ Early PC can help manage uncertainty, facilitate complex decision making, and support ACP without diminishing hope for

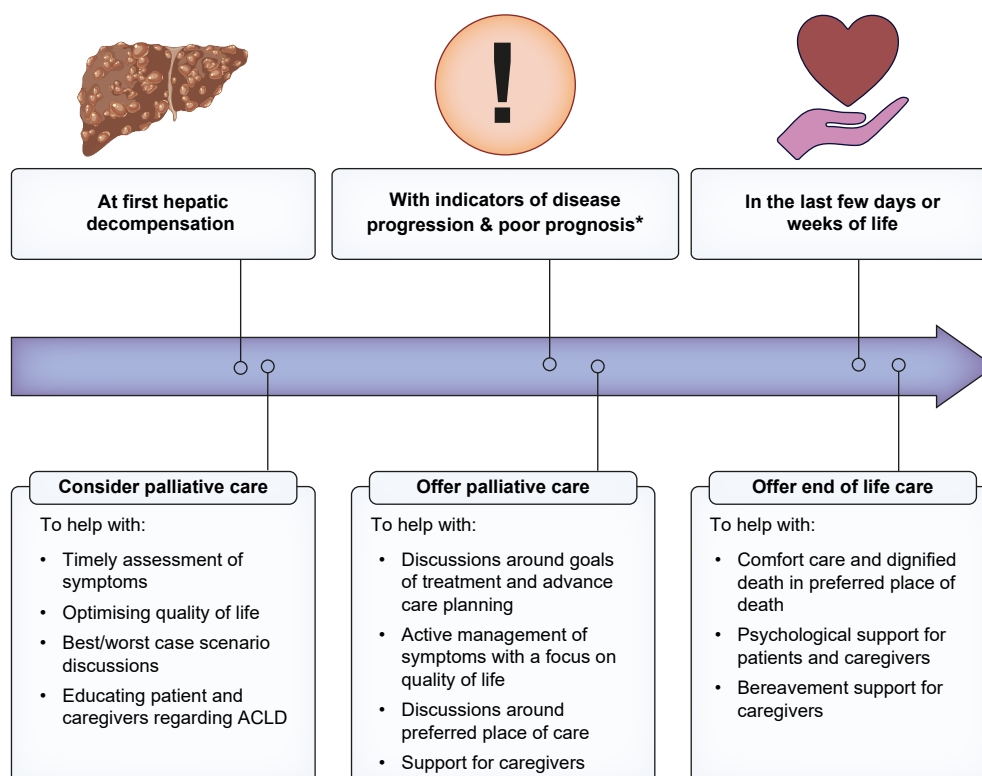


Fig. 1. When to consider and offer palliative care in ACLD. *Repeated hospitalisations (especially with worsening liver prognostic scores) and/or presence of refractory ascites, frailty/poor performance status and ongoing alcohol use. Prognostic tools should also include the 'surprise question', Bristol prognostic score, and the SPICT (supportive and palliative care indicators tool). ACLD, advanced chronic liver disease.

transplantation. It is therefore essential to establish parallel care pathways early in this group, in which curative and palliative approaches coexist. This allows patients and families to dynamically discuss best and worst-case scenarios and to adjust care goals accordingly.⁴¹

Patients with first presentation of decompensated ALD

Another group is those with first presentation of decompensated ALD where the disease course is even more uncertain, as some may recompensate following abstinence. PC is often not considered for this group,¹¹⁴ and the stigma associated with alcohol often complicates care, as most patients are ineligible for transplantation. However, a large retrospective study in ALD has shown that initiating PC is associated with shorter hospital days and lower rates of readmission and hospital costs.¹¹⁴ Therefore, multidisciplinary collaboration between hepatologists, addiction specialists, mental health professionals, and PC teams can make a significant difference to these patients and should be encouraged.

Patients with HCC

A third group are those with HCC. The prognosis for patients with more advanced HCC (BCLC B/C) is poor, with median survival varying between less than 12 and 40 months. In patients with BCLC stage D disease, as survival is only 2–4 months, palliative interventions are often the only option.¹¹⁵

The expansion of treatment options – including immunotherapy, microwave ablation, transarterial chemoembolisation,

and intra-arterial radiotherapy – has made downstaging to a curative stage increasingly possible. This has resulted in longer progression-free and overall survival, making it more challenging to predict outcomes. Finally, there is a lack of prospective studies in this patient population. Nonetheless, there are no indications that the benefits of PC described previously do not also apply to patients with HCC;⁸⁷ on the contrary, PC interventions can positively impact **symptom burden and HRQoL** in patients with HCC.⁹⁵

Thus, as recommended for advanced solid cancers, patients with advanced HCC – particularly those with an expected overall survival of less than two years – should be referred early in the disease course to specialised interdisciplinary PC teams, in parallel with active anti-tumour treatment.¹¹⁶

Why is PC in ACLD suboptimal and how can this be improved?

PC consultations occur infrequently in ACLD,^{117,118} often very late, and frequently in the final days or weeks of life.⁸⁸ Hospice and PC service utilisation vary geographically, with the highest availability and affordability in high-income countries, and lowest use in Africa, China, and India.¹¹⁹ There is, however, a rising trend, notably in the US, with PC utilisation increasing from about one-third of hospitalised patients with ACLD (2006–2013),^{89,96} to around 50% (2016–2020).⁹⁷

Factors associated with a higher likelihood of receiving PC include older age, DNACPR (do-not-attempt cardiopulmonary

resuscitation) requests, the presence of HCC or metastatic cancer, higher acute-on-chronic liver failure grade, and admission to teaching hospitals. In contrast, liver transplant candidacy, African American/Hispanic/Asian race, and lower socioeconomic status were factors associated with a lower referral rate.^{88,89,96,97,120}

Access to PC is hampered by barriers at the patient, provider, and system level (Fig. 2).^{77,121–125} These include a heterogeneous cohort with an unpredictable disease trajectory,^{126,127} making it difficult to estimate the point of irreversible liver deterioration.¹²³ Secondly, the stigma and misconception of PC being synonymous with EoLC may be seen as incompatible with ongoing medical treatments. It may prevent PC referral for potential transplant candidates, as it is perceived to be 'giving up' or contradicting expectations and goals,^{122,123,128} potentially resulting in lower quality PC for these patients.¹²⁹ Thirdly, the role of PC in patients with ACLD is ill-defined, poorly integrated within hepatology services, and insufficiently addressed in hepatology guidelines (possibly due to the paucity of high-quality RCTs).⁷⁷ Unlike patients with cancer, where symptom management by PC specialists is often an integral part of the treatment plan,¹³⁰ the complex nature of ACLD symptoms rather ties their management to liver specialists. Ineffective communication – due to the presence of HE,¹³¹ limited time and resources, and low skills or confidence to discuss sensitive topics (i.e. prognosis, end of life, ACP, PC) – may result in higher symptom burden, poorer HRQoL, and unrealistic expectations regarding transplant eligibility, treatment effectiveness, goals, and prognosis.^{77,101,122,123,132}

Overcoming these barriers is paramount to improving integration of PC (Fig. 2), this being one of the key elements of

value-based patient-centred care in the underserved ACLD population.¹²⁵ Strategies include delivery of generalist PC by hepatology teams after adequate training, including serious illness communication, symptom management, and ACP.¹³³ A virtual PC training programme for hepatologists has been shown to improve knowledge and confidence to deliver generalist PC.¹³⁴ Education of clinical staff and implementation of standardised processes improves ACP completion, resulting in shorter hospital stays.¹³⁵ The development of joint educational programmes by hepatology and palliative medicine societies could also help to improve the training of clinicians from both specialties caring for patients with ACLD.¹³⁶ Moreover, implementation of standardised and clinically validated PC consultation criteria, as well as the routine use of clinical tools such as SPICt and the Bristol prognostic score,^{111,112} may improve identification and referral to specialist PC.^{137,138} Other measures include addressing misperceptions of specialist PC among hepatologists, implementing novel PC delivery models (e.g. integrated specialist PC in hepatology and transplantation outpatient care), and integrating PC into MDTs (Fig. 2).^{77,93,133} Finally, the need for palliative RCTs to measure the efficacy of different interventions in ACLD cannot be overemphasised.

Summary statement

In patients with ACLD, PC may be associated with reduced physical and psychological symptom burden, improved ACP and EoLC, reduced healthcare resource utilisation, and improved caregiver support. Key barriers for integrating PC into the management of patients with ACLD may depend on

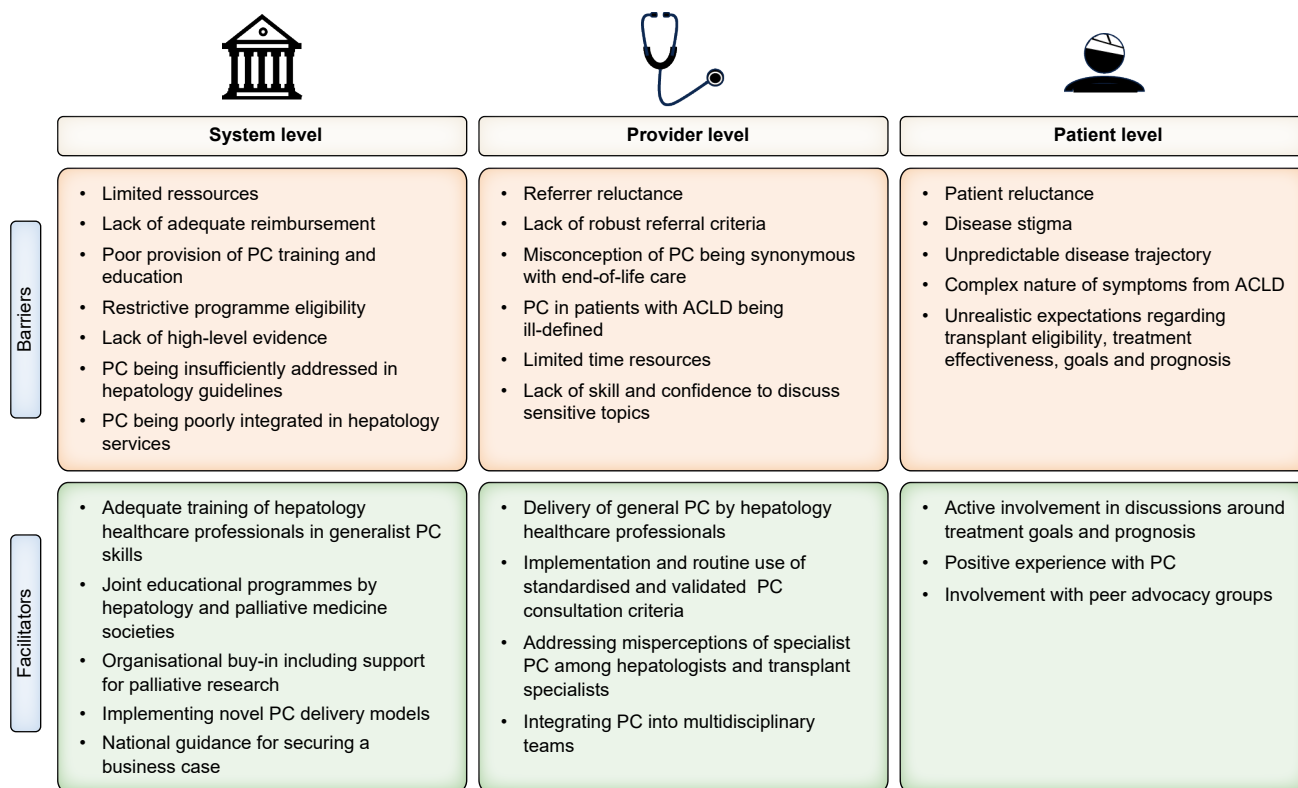


Fig. 2. Barriers and facilitators to provision of palliative care in ACLD. ACLD, advanced chronic liver disease; PC, palliative care.

country and region, and include the unpredictable disease trajectory, late referral, perceptual barriers among both providers and patients, lack of knowledge, training, and confidence among hepatology specialists, challenges in communication, and lack of adequate reimbursement and resources.

Recommendations

- Measures to improve PC utilisation should be implemented in ACLD across all ethnicities and socioeconomic groups. This includes targeted training and education of hepatology providers, provision of generalist PC by hepatology HCPs, early identification and referral of patients to specialist PC, implementing integrated specialist PC into multiprofessional care models, combating stigma and misconceptions around PC, and improving communication around prognosis and EoLC.
- Early integration of PC for patients with ACLD should be pursued, irrespective of transplant eligibility and potential for recompensation, as this is likely to improve HRQoL and could provide support for patients and their caregivers. Parallel planning is recommended given the uncertainties around prognosis and disease trajectory.
- Routine use of prognostic scoring is recommended to enable assessment of transplant eligibility, help communicate information effectively to patients and caregivers and to ensure that PC can be delivered in a timely manner.

ACP/integration of PC

When and in which patients with ACLD should ACP be discussed and by whom?

Key components of ACP include several decisions associated with ceiling of care and life-sustaining interventions. Patients with ACLD and their families are frequently unprepared to face difficult decisions resulting from critical life-threatening complications¹¹⁷ that may occur unexpectedly.

ACP is a pre-emptive, individualised, and collaborative process of decision making, in which patients and HCPs work together to identify and document patient preferences for future medical care, so that it is consistent with their goals and values in the context of a serious life-limiting disease.^{9,139} ACP aligns with the ethical principles of medicine because the welfare of the patient is always the primary concern of the healthcare team. An MDT approach is needed to provide PC, and this team should also be involved throughout the entire process, including supporting ACP. There is well-established consensus regarding the universal principles of ACP, including that the person is central to developing and agreeing their ACP.¹⁴⁰ Patients' decisions and priorities are paramount and should be respected. Consideration must also be given to family members, especially when the patient is receiving home-based PC. The goal of ACP is to ensure that a person's values, preferences, and wishes for future medical care are understood, respected, and followed.

Patients with decompensated ACLD have a median life expectancy of approximately 2 years in the absence of liver transplantation.^{141,142} They are often exposed to higher rates of intensive healthcare interventions at EoL compared to patients with other chronic life-limiting conditions, underscoring the importance of timely ACP.^{143,144} Given the unpredictable trajectory of the disease, ACP should start early in the course of decompensated ACLD, before the onset of critical conditions including HE, which can impact communication and decision-making capacity.^{143,145} A systematic review suggests that appropriate use of PC in ACLD can prompt timely ACP.⁸³

ACP does not preclude curative treatments, but should be integrated into the medical management of ACLD, delivered concurrently with disease-targeted therapy, including liver transplantation. However, patients with ACLD – including those who die while on the transplant waiting list, or are delisted – rarely receive timely ACP discussions.^{129,146,147}

ACP discussions early in the course of an incurable illness have been shown to improve the quality of EoLC for patients and reduce caregiver stress and anxiety.^{148,149} In patients with ACLD, two small prospective pilot studies focusing on ACP education and an ACP video decision support tool, showed improved ACP completion and shorter hospital stay in patients whose advance directive specified nonaggressive goals.^{135,150} ACP was well accepted, and patients in the intervention arm had greater knowledge about EoLC and were less likely to receive CPR compared to the control arm, in which only a verbal narrative was received^{135,150} (see also Table 5).

Facilitating ACP is an important component of caring for patients with ACLD who have limited life expectancy, and should be available to all suitable patients. It is best delivered iteratively by HCPs known to the patient. Hepatology HCPs routinely deliver some general components of PC by managing symptoms and complications of liver disease,¹⁵¹ as well as by conducting discussions around disease understanding, prognostic uncertainty and exploration of patients' wishes and barriers to ACP, and how these may be overcome. Many patients with ACLD prefer to have conversations about the outcome of their illness with their hepatology HCP, having developed a trusted therapeutic relationship.¹⁵²

Not all hepatology clinicians, however, engage in timely ACP. An American study reported that 81% of patients with decompensated ACLD had never discussed their EoLC wishes with their hepatologists.¹³² Potential barriers include limited EoL communication and cultural competency training, time constraints, fear of undermining the clinician-patient relationship, and a focus on liver transplantation rather than preparing for other, often less favourable, outcomes.^{101,153} Additional barriers include lack of education around documentation processes and the associated administrative burden. An earlier quality improvement study focusing on champions, education, electronic health record templates, and workflow changes showed an increase in, and earlier completion of, ACP.¹³⁵ Barriers also exist at the patient level, including poor understanding of disease trajectory and unrealistic hope for a liver transplant.^{101,131} This underscores the need for MDT working and training to enhance the skills required to deliver effective ACP.¹⁵²

Through an ongoing empathic relationship, patients are invited to discuss their healthcare preferences openly and without stigma.¹⁵⁴ Patients must be, and feel, fully involved in the process and should perceive themselves as having control over their destiny, particularly in terms of avoiding suffering. Families and informal caregivers should also be invited to participate in ACP, as they are essential to the process.¹⁵⁵ ACP is a personalised and holistic approach that respects the patient's wishes and may include spiritual counselling for some patients.¹⁵⁶ A structured communication framework for serious illness conversations with patients with ACLD is shown in Fig. 3 and Table 4.^{9,133,157,158} This can also include the REMAP (Reframe; Expect emotion; Map out patients' goals; Align with goals; Propose a plan/treatment) framework¹⁵⁸ which is especially useful when there is a clinical change. Other ACP frameworks include PREPARE,¹⁵⁹ and for values assessments, Patient Priorities Care.¹⁶⁰

Patients should be able to consider the possibility of drawing up a living will (advance directive) or appointing a legal representative (surrogate decision maker/lasting power of attorney). Patients' wishes should prevail if they lose capacity,

and this should be clearly explained to the legal representative, even if they are a family member. Patients should be aware that they have autonomy over their lives, even if they are unable to make decisions, due to the inexorable progression of liver disease or a concomitant condition (e.g. dementia). ACP may include dignity therapy; in this clinically effective psychotherapy, the fundamental needs of dying patients are addressed.^{161,162}

Summary statement

ACP is an individualised, iterative and collaborative process of decision making, usually involving hepatology HCPs with support from a multidisciplinary team. The key components of ACP include several decisions associated with ceiling of care and life-sustaining interventions. The goal of ACP is to ensure that a person's values, preferences, and wishes for future medical care are understood, respected, and followed, thus improving EoL experience for patients and their caregivers. Patients, caregivers and HCPs should work together to ensure that ACP is considered early during the course of decompensated ACLD. ACP

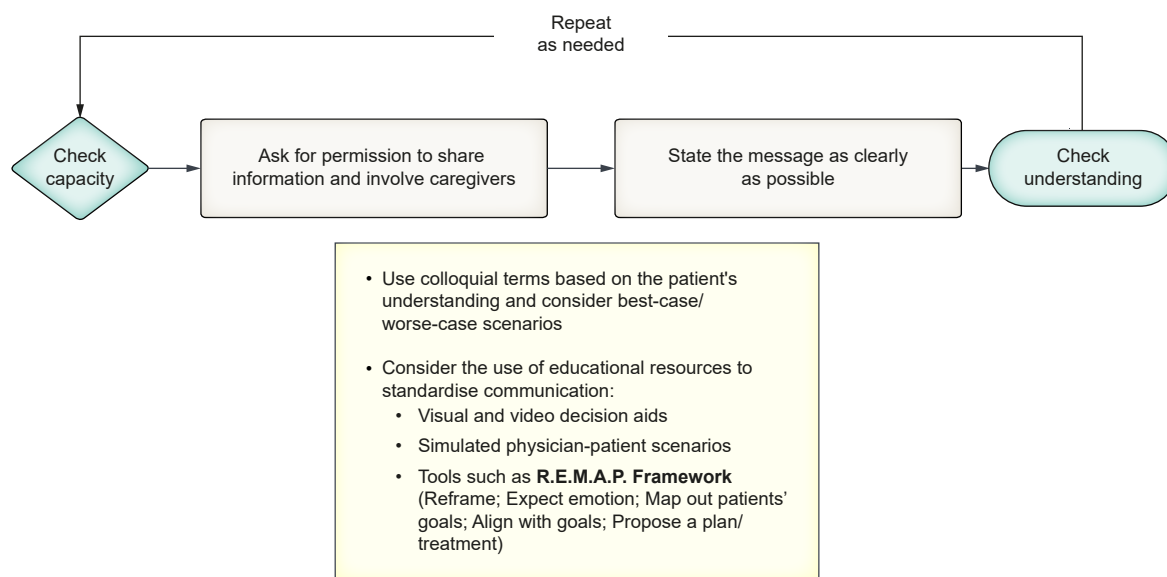


Fig. 3. Structured communication framework for serious illness conversations (advance care planning) in patients with advanced chronic liver disease.

Table 4. Prompts for initiating serious illness conversations.^{157,158}

Prompts	
Opening the conversation/asking permissions	"I'd like to spend some time today discussing how things are going with your liver disease and planning next steps. Would that be alright with you?" "I wonder if it would be OK for us to spend some time talking about the future with respect to your liver condition. Would that be alright with you?"
Exploring patient understanding	"What's your understanding of where things are with your liver condition at the moment?" "What have you heard from the team about how things are with your liver disease right now?" "How much information would like from me – some people like a lot of details, but others might just want the big picture"
Explaining uncertainty	"It can be difficult to predict what the future holds in patients with liver disease. Would it be helpful for me to talk through the best-case and worst-case scenarios?"
Exploring goals	"When you think about the future, what are the most important things to you?"
Exploring ceilings of care	"If things start to deteriorate with your health, have you had any thoughts around what treatments would, or would not be right for you?"

Recommendations

- Through an ongoing empathic relationship with patients and caregivers, ACP should involve identifying and documenting patients' preferences for future medical care that align with their goals and values in the context of a serious life-limiting disease. This can include drawing up a living will or appointing a legal representative.
- Due to the unpredictable disease trajectory in ACLD, ACP should be initiated early in the course of decompensated disease, before the onset of critical events which may compromise decision-making capacity.
- ACP should be delivered by an HCP well known to the patient, with support from a MDT.
- ACP should be integrated into the medical management of ACLD and does not preclude curative disease-targeted therapy, including liver transplantation, which can be offered in parallel.

discussions can also be integrated into conversations around liver transplant on a case-by-case basis. Empathetic and compassionate communication is essential for effective ACP and should follow a structured framework for serious illness conversations.

Caregiver support

What impact does ACLD have on caregivers?

Informal caregivers of patients with ACLD, often family members, play a crucial support role but are also fundamentally affected themselves.^{163,164} Studies show increased levels of anxiety, depression, fatigue, and decreased social functioning, comparable to caregivers of patients with cancer.¹⁶⁵

Worsening liver disease results in progressive cognitive and physical limitations and increased dependence,¹⁶⁶ with informal caregivers experiencing increasing physical, emotional, and social challenges.^{30,39,167} This can lead to social isolation, with de-prioritisation of their own needs.⁸² Additionally, due to the fluctuating nature of ACLD, caregivers must constantly adapt to changes in the patient's condition without warning or support,¹⁶⁸ thus increasing caregiver burden.

Recurrent ascites increases stress due to the need for frequent hospital visits and increased support with daily activities, with informal caregivers showing lower physical and social functioning compared to the general population.⁷³ HE is associated with significant psychological and emotional distress amongst caregivers – including increased levels of anxiety and depression.^{169–171} The HRQoL of patients and their caregivers appears to be closely linked, with deterioration in one often mirrored in the other.⁷³ Studies involving patient-caregiver dyads have also shown that patient and caregiver stress is both prevalent and interdependent. An American study demonstrated that caregiver anxiety was predictive of patient depression.¹⁷² This correlation emphasises the importance of addressing the needs of both patients and caregivers. Early inclusion of PC can promote effective

symptom control and is key to improving patients' HRQoL and preventing distress among family members.^{9,47} A PC intervention within a surgical intensive care unit managing liver transplants allowed patients and families more time together and gave them the opportunity to say goodbye.¹⁷³

In addition to physical and mental health, social and financial problems need addressing.⁶⁶ Caregivers often experience additional stress due to changes in patients' behaviour with advancing disease,¹⁶⁴ or feelings of shame when disclosing the patient's liver disease,¹⁷⁴ as well as significant financial burden. This includes increased healthcare costs and potential loss of income due to caring responsibilities.^{175,176} This economic burden can have a negative impact on HRQoL and general well-being, and is likely to affect many patients with ACLD and their caregivers. A multidisciplinary approach that incorporates PC for the comprehensive management of ACLD, while recognising the burden on caregivers, is therefore crucial.⁴⁷ Education, increased support from hepatology HCPs, and greater public awareness are needed to eliminate misconceptions and reduce the stigma associated with liver disease among patients and caregivers.

How can we best support informal caregivers?

The differing needs of patients and caregivers underline the importance of providing targeted support by first identifying the most pressing problems, and then developing tailored interventions to address them effectively.

However, there is still lack of clarity about when, and how to assess caregiver burden, largely due to the scarcity of evidence-based interventions. To maintain caregivers as a vital resource and promote their well-being, it is crucial to recognise their important role, and to address the challenges they face to ensure they receive the support they need.⁹ There is currently no clear agreement on the appropriate time, method, or HCP for this task.¹⁶⁵ It is important to recognise family members as a valued resource at an early stage of the disease, while ensuring effective communication between HCPs, patients, and families to support ACP and align care with patients' values and preferences.¹¹⁸

Structured assessment tools are beneficial in assessing caregiver burden and related issues such as depression, anxiety, and sleep problems and include the ZBI (Zarit burden interview),^{169,177} the CRRS (caregiver roles and responsibilities scale),¹⁷⁸ and the CRA (caregiver reaction assessment).¹⁷⁹ Due to the complexity of caregivers' needs and the lack of RCTs, a flexible approach with a combination of different validated instruments is recommended.¹⁷⁷

A recent RCT examined two mindfulness methods (written emotional disclosure and resilience training) compared to a control group and found a significant improvement in caregivers' wellbeing in the mindfulness groups.¹⁸⁰ Another study showed that a short course of mindfulness and supportive group therapy significantly reduced caregiver burden and improved their sleep quality.¹⁸¹ Similarly, an evaluation of the perspectives of inpatients with cirrhosis and their caregivers on the use of health information technology found that tailored technological interventions can improve caregiver engagement and support.¹⁶⁹ In contrast, an uncertainty self-management telephone intervention delivered by

trained nurses or social workers did not improve caregiver outcomes in an RCT that included liver transplant candidates and their caregivers.¹⁸² Two additional RCTs investigating palliative long-term abdominal drains (LTADs) in refractory ascites due to ACLD have also emphasised the importance of incorporating the experience of caregivers^{183–185}.

Summary statement

Informal caregivers play an essential and often under-recognised role in supporting patients with ACLD. Caregivers frequently face increasing emotional, physical, financial, and social burdens with anxiety, depression, and diminished HRQoL. The experience of the caregiver is closely linked with the well-being of the patient. There is limited guidance on when, and how, to assess caregiver burden, and few evidence-based interventions exist to address their needs. However, consensus exists regarding the need for early integration of PC, the use of structured assessment tools, and targeted psychosocial support to help reduce caregiver burden. A multidisciplinary approach that includes caregivers as key

Recommendations

- To support both patient and caregiver well-being, hepatology HCPs should acknowledge caregivers as essential partners from the time of diagnosis of ACLD, and maintain ongoing involvement, particularly during periods of disease progression.
- Validated tools should be used to assess caregiver physical, emotional, financial, and psychological needs. Clinical guidance should be provided on how best to implement and interpret these tools.
- Targeted support based on individual caregiver stressors – which may include education, mental health resources, and practical assistance to reduce anxiety, depression, and fatigue – should be offered.
- Using a multidisciplinary approach, caregivers should be involved in ACP and PC strategies to ensure care aligns with patient values, and to reduce caregiver distress.
- Caregiver participation in palliative clinical trials should be encouraged to establish evidenced-based interventions that can improve caregiver experience and HRQoL.

partners in care planning is critical to improving outcomes for the patient-caregiver dyad.

Aspirations for a PC service in ACLD

What are the core components of good PC in ACLD services?

Access to PC is a fundamental human right,¹⁸⁶ and is recognised by the WHO as an international policy priority.¹⁸⁷ It is incumbent upon services caring for patients with ACLD to provide PC, given the high physical and psychological burdens associated with the condition. Whilst there will be resource-

dependent heterogeneity in the level of PC services provided, the following section describes some of the core components and possible strategies for the design of a palliative hepatology service.

Formal and routine assessment of prognosis to ensure timely identification of patients who will benefit from PC

As previously stated, prognosis in ACLD is frequently unpredictable and the perception that PC is synonymous with EoLC can act as a barrier to timely interventions. Physicians are frequently overly optimistic in their predictions around survival, potentially accentuating issues around late (and therefore lower quality) PC interventions.¹⁸⁸

Systems for discussing prognosis and ACP with patients and caregivers across healthcare sectors

Information around prognosis and disease trajectory prior to significant clinical deterioration is valued highly by patients and caregivers,¹³¹ who typically want more information about the disease.¹⁶⁷ It is important therefore, that this is communicated in a timely manner. Patients consistently report that discussions around prognosis are better delivered by an HCP known to them, and hepatologists/liver nurse specialists are well placed to facilitate these discussions. Services should look to allocate sufficient time for this so that discussions are not rushed.

ACP discussions can include, but are not limited to, the appropriateness of intensive care admission, CPR, emergency endoscopy, thresholds for acute admission to hospital (as opposed to community-based care) and preferred place of death. Good ACP is associated strongly with increased patient satisfaction, and improved EoLC.¹⁸⁹ Services should ensure that ACP discussions are documented and communicated across healthcare boundaries. Poor prognosis letters to primary care physicians,¹⁹⁰ and clear documentation in hospital/electronic records of ceilings of care, are highly valued and can potentially avoid futile invasive interventions towards the EoL. Conversely, such communications can guard against nihilism/denial of appropriate intensive care from out of hours emergency/intensive care teams in other patients (e.g. patients with ACLD listed for transplantation). Additional tools include “prompts” or “add-ons” to electronic patient records that can help facilitate high-quality serious illness communication.¹⁹¹

Ambulatory services which reduce the need for inpatient care

The model of care for patients with ACLD has traditionally involved recurrent, unplanned hospital admissions of increasing frequency within the last year of life, though this is frequently considered incompatible with the needs of patients and caregivers towards EoL. Care delivered outside the setting of an acute hospital admission is valued highly by patients and caregivers.⁸² A study of patients who died from ACLD demonstrated that use of an ambulatory large volume paracentesis unit within the last year of life was associated with significantly lower emergency hospital admissions/readmission/inpatient bed days/healthcare costs and an increased chance of death occurring outside hospital, potentially indicating a further association with improved

ACP.¹⁹² Ambulatory services can also be utilised to facilitate rapid and iterative outpatient clinical review of unstable patients (e.g. monitoring renal function or administration of human albumin solution). A functioning ambulatory unit is likely to be cost-effective, given associated savings in inpatient care, and should form part of a high-quality palliative hepatology service.

Services which address physical and psychological symptoms including frailty

Addressing physical and psychological symptoms including frailty

Physical and psychological symptoms have been identified as extremely important by patients with ACLD, and proactively addressing them has been identified as a marker of high-quality liver care.¹⁹³ Aside from direct symptoms of decompensation, the presence of poor sleep, muscle spasms, pruritus, pain and sexual dysfunction (where appropriate) should be explored (see section on [symptom burden and HRQoL](#)). However, services should also look to develop links with specialist PC for patients with complex symptom needs (e.g. severe pain). The liver frailty index and frequency of falls are associated with markedly increased mortality and reduced HRQoL in patients with ACLD.^{59,194} Physical rehabilitation and occupational therapy programmes may reduce physical frailty and (through maximising/optimising independence) improve HRQoL. The EXALT RCT is investigating home-based exercise programmes before and after liver transplantation.¹⁹⁵ Optimising nutrition can lead to improvements in HRQoL, physical function,¹⁹⁶ and cognition.^{196,197} Services providing care for patients with ACLD should establish links with allied HCPs

(e.g. dietitians, physiotherapists and occupational therapists) so that these facets of care can also be optimised.

Signposting and systems to support caregivers

A considerable number of caregivers of patients with ACLD (most being partners or spouses),¹⁹⁸ need to give up or significantly reduce work, adding financial difficulties to an already distressing situation of escalating physical and psychological need. Factors associated with increased caregiver burden in ACLD, include HE, low income, active alcohol use, and the presence of additional dependents (e.g. children) in the household,¹⁹⁹ (see section on [caregiver support](#)). Services providing PC should also be attuned to recognising caregiver burden and provide signposting/community links for caregiver support.

Multidisciplinary/interprofessional care

Addressing PC needs comprehensively requires a wide breadth of expertise. High-quality services will have access to input from a range of allied HCPs within acute and community settings. MDT meetings are one way of providing wide-ranging expertise to patients with ACLD. MDTs have the potential to improve co-ordination of care between the hospital and the community, inform ACP discussions, and triage patients with specific or complex needs to the appropriate HCP. The composition of an MDT may include (alongside hepatologists/hepatology nurse specialists), specialist PC clinicians, dietitians, occupational therapists, physiotherapists, community alcohol teams, social workers, a community hospice representative, and spiritual care. For each patient, the MDT may

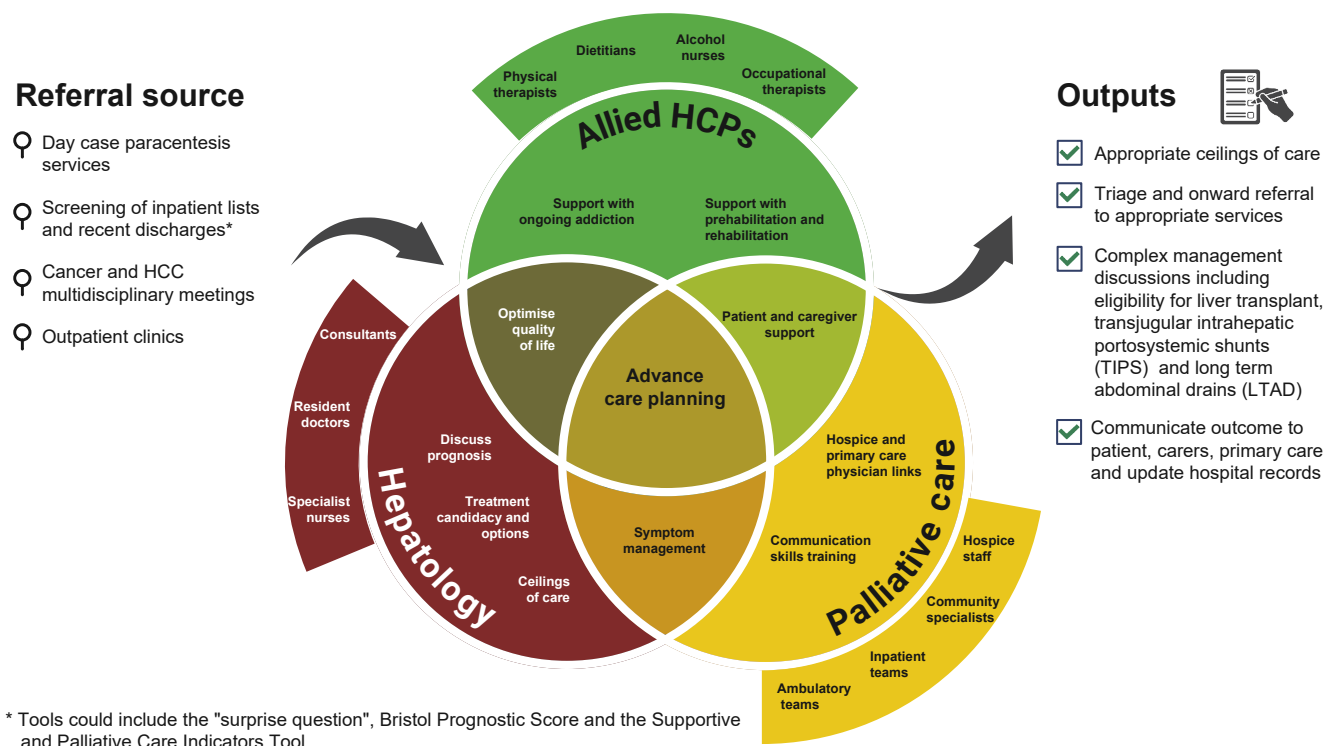


Fig. 4. Suggested structure of advanced chronic liver disease multidisciplinary team. HCC, hepatocellular carcinoma; HCP, healthcare professionals.

discuss optimum medical management (including transplant candidacy), an appropriate emergency treatment plan and ceiling of care (which may inform future ACP discussions) and consider factors which may improve HRQoL. Management advice from allied HCPs can be provided, and patients with specific needs can be triaged to the appropriate specialist – for example, physiotherapy for frailty in patients on the transplant waiting list, dietetics for malnutrition, specialist PC for complex physical symptoms, or primary care for patients wishing to transfer their care to the community. An example of a possible MDT structure is shown in Fig. 4.

Services running an ACLD MDT should have systems for sharing the outcome of the discussion (including decisions around ceiling of care etc.) across healthcare sectors (including the emergency department and community healthcare), as well as ensuring a mechanism to feed back to the patient. An example of an ACLD MDT outcome proforma is shown in Fig. S1. The resource implications for services establishing an ACLD MDT have been modelled in a UK setting, and the model predicts that such services would be cost saving over time.⁹⁸

What metrics for audit and quality improvement should be considered in units providing PC in ACLD?

Liver services should iteratively monitor the quality of their PC services in order to drive ongoing improvements and identify possible gaps in care. Although metrics for quality of PC in ACLD have not been directly validated against patient-reported outcomes, the available evidence suggests that the following could be embedded into the governance procedures of organisations providing high-quality palliative hepatology.

Mortality reviews

Although mortality reviews are well established within wider governance processes, they typically focus on whether any lifesaving or life-prolonging interventions were overlooked. Services should also be encouraged to review the quality of death including preferred place of death, and potential missed opportunities for PC interventions and ACP.

Utilisation of ambulatory services

Enrolment and uptake of ambulatory large volume paracentesis procedures can be monitored as a surrogate for uptake and utilisation of these services.

Hospital readmission rates within 30 days

Whilst some readmissions to hospital are necessary, there is also an association between increased morbidity and inadequate community/ambulatory care.²⁰⁰ Monitoring of readmission rates and scrutiny of reasons for readmission could be used by services to improve quality of discharge planning in patients approaching EoL.

Proportion of patients with ACLD dying in hospital who have a documented ACP/resuscitation status at the point of terminal admission

This metric would monitor the uptake of ACP (+/- the reach of the advanced liver disease MDT) among the hospitals' ACLD population and potentially highlight missed opportunities for advanced disease discussions within the last year of life.

Service questionnaires for patients and families with ACLD

ACLD services should iteratively monitor patient and caregiver feedback, in order to highlight both areas for improvement as well as areas of good practice. A useful tool that can be used is the "heard and understood" survey.²⁰¹

Equality impact assessment

It is essential that services perform equality impact assessments to ensure that care is delivered in an equitable manner irrespective of ethnicity and socioeconomic status.

Summary statement

Robust systems for identifying and managing the PC needs of individuals with ACLD should represent a core component of any high-quality liver service. Access to a regular MDT, including specialist PC and allied HCPs, could enable more coordinated PC for individuals with ACLD. Iterative and objective assessment of prognosis increases the likelihood of patients receiving timely PC, and services should routinely integrate this into patient care. Prognostic information should be shared across healthcare settings, to facilitate joined-up care. Ambulatory care is valued by patients and caregivers with ACLD, and is associated with improved outcomes in the last year of life. HCPs should monitor and continuously improve their service, through mortality reviews, patient and caregiver feedback, and scrutiny of resource use.

Recommendations

- Systems for the provision of PC should represent a core component of any service treating patients with ACLD. They should iteratively and objectively assess and discuss the prognosis of patients with ACLD to identify those likely to benefit from PC interventions and ACP.
- Systems should be established which share information around prognosis and ACP across healthcare sectors.
- Services should:
 - Offer ambulatory services to patients with ACLD.
 - Include regular MDT meetings to optimise physical and psychological symptoms (all associated with poor HRQoL) and should also be able to signpost caregivers to support.
 - Monitor and continuously improve the effectiveness and quality of the care provided for individuals with ACLD.

Palliative research

What are the barriers to conducting palliative research in ACLD?

Although PC is embedded in many chronic, non-cancer disease guidelines,²⁰² an important barrier to the delivery of timely PC in ACLD is the limited evidence base, which remains a clear unmet need. This population presents unique challenges for conducting research, which might explain the perceived scepticism and anxieties by funders in supporting palliative hepatology research. Barriers and facilitators to palliative hepatology research are discussed below and summarised in Fig 5. Table 5 and S3 summarise recent studies in palliative hepatology.⁷⁷

Table 5. Recent palliative interventional studies in advanced chronic liver disease. Adapted from Verma S et al. *J Hepatol.* 2023;79:1236-1253.⁷⁷

Study/country/duration	Type of study, intervention and primary outcome	Inclusion/exclusion criteria	Sample size	Study status	Results	Barriers/facilitators
Veteran-Centered Care for Advanced Liver Disease (Vet-CALD) (Vet-CALD) ²³⁸ United States NCT06068491 2024-2027	• Multicentre RCT • Usual care vs. Vet-CALD intervention: centralised research care counsellor who will work with patients by telehealth) to assess and cultivate their understanding of their illness and identify personal healthcare goals.	• Adults with advanced liver disease	450	Ongoing	Ongoing	
LiverPAL: A Trial of Inpatient Palliative Care for Patients With Advanced Liver Disease (LiverPAL) ²³⁹ United States NCT05998330 Sept 2023-July 2027	• Single-centre RCT • Usual care vs. intervention: integrating early PC with usual hepatology care to evaluate and treat symptoms, enhance their illness and prognostic understanding, support their coping, and coordinate serious illness, transitional, and end-of-life care • Primary outcome is HRQoL assessed using Functional Assessment of Chronic Illness Therapy - Palliative Care, FACIT-Pal) at week 4	• Includes hospitalised patients with decompensated cirrhosis • Excludes if prior transplantation, uncontrolled HE, advanced HCC, serious comorbidity and already receiving PC	200	Ongoing	Ongoing	
Integrating palliative care into liver cancer pathways ²⁴⁰ Australia ACTRN12623000010695 July 2022-Jul 2031 Four sites	• Multicentre cluster RCT with 5-year follow-up • Intervention will include completing liver-specific ESAS and EORTC QoL questionnaire and caregivers CSNST – if scores above threshold reached referral to PC triggered. • Primary outcome is mean change in liver-specific ESAS • Includes a qualitative sub study	• Includes patients and caregivers with cirrhosis and HCC BCLC stage A-C • Excludes those with BCLC stage D, inability to consent and already receiving PC	386	Ongoing	Ongoing	
Palliative Care for Patients with Liver Cirrhosis (LiverCare) ²⁴¹ Denmark NCT05431946 Aug 2022 -Aug 2026	• Multicentre observational case-controlled study • Intervention: advanced care planning • Primary outcome: Intra-subject change in patient burden (Hospital Anxiety and Depression Scale) (from date of inclusion until death assessed up to 100 months)	• Includes patients with cirrhosis with two or more items checked on SPICT, expressed desire for PC from patient/caregiver and ability to give informed consent • Excluded if ongoing PC, unable to consent and significant comorbidity	200	Ongoing	Ongoing	
Palliative Long-term Abdominal Drains vs. Repeated Drainage in Untreatable Ascites Due to Advanced Cirrhosis: A Randomised Controlled Trial (REDUCe 2 Study) ¹⁸⁵ United Kingdom ISRCTN26993825 May 2022-Jan 2027 35 sites	• Multicentre RCT • Palliative LTAD vs. LVP 3 month follow-up • Primary outcome; HRQoL assessed at 3 months using SFLDQoL questionnaire	• Includes patients and caregivers with cirrhosis and refractory ascites and able to consent • Excluded if candidates for transplantation/TIPS, unable to consent, active infection and chylous/loculated ascites	310	Ongoing	Ongoing, protocol published	• Challenges identified in feasibility study¹⁷⁴ addressed • Ongoing barriers include offering intervention outside of trial settings

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Table 5. (continued)

Study/country/duration	Type of study, intervention and primary outcome	Inclusion/exclusion criteria	Sample size	Study status	Results	Barriers/facilitators
Introducing Palliative Care (PC) Within the Treatment of End Stage Liver Disease (ESLD) (PAL-LIVER) ²¹¹ United States NCT03540771 Jan 2019-May 2025 19 sites	- Multicentre cluster RCT 3 month follow-up - PC delivered by PC trained providers vs. PC trained provider vs. delivered by trained hepatologists (online training on communication, psychosocial support, goals of care, symptom management - physical and psychological, spiritual care, hospice, survivorship, caregiver support) - Providers use PC checklist after each intervention visit, to assure delivery of key elements of PC. - Primary outcome: change in HRQoL from baseline to 3 months assessed by FACT-Hep questionnaire	- Includes patients with cirrhosis or HCC (not currently evaluated for transplant), with a caregiver willing to participate. - Excluded if MELD >30 or life expectancy <6 months	1,260	Completed. Protocol published	- Awaited - PC training of hepatologists demonstrated success	- Achieved recruitment target - Had a feasibility trial prior to main study - Multisite trial
Tunnelled Peritoneal Catheter for Refractory Ascites in Cirrhosis: A Randomized Case-Series (PETRA) ²⁰⁵ Denmark NCT03027635 Jan 2017-May 2019	- Single-centre RCT - LTAD vs. LVP - Primary outcome: Time to first paracentesis. All received prophylactic antibiotics for study duration	- Included patients with cirrhosis and refractory ascites and at least 3 months expected survival - Excluded if TIPS eligible, serum creatinine >135 µmol/L, overt HE, variceal bleeding, active infection and loculated ascites	32	Terminated due to slow recruitment. No published protocol	- Study published - N = 13 recruited (LTAD n = 6, LVP n = 7) - In LTAD group only one patient needed further LVP - LTAD colonized in all. One patient in each group developed peritonitis	- Screening failures? restrictive inclusion criteria - Clinical deterioration precluded recruitment - Offering intervention outside of trial setting
Peritoneal Dialysis Catheters for the Treatment of Refractory Ascites ²⁰⁶ Canada NCT02975726 Jan 2017 – Feb 2019	- Single-centre RCT 2-month follow-up - Peritoneal device vs. LVP - Primary outcome: Improvement of 10 points in the physical component score (PCS) of the Short Form-36 (SF-36) at 2 months.	- Included patients with cirrhosis and refractory ascites - Excluded those with prior SBP, INR >1.5, plat <50x10⁹/L, HIV positive, expected survival <6 months, MELD >30, transplant candidates and severe HE	50	Terminated due to slow recruitment. No published protocol	Not available as only two patients recruited	- Perceived negative impact on future transplant - Restrictive inclusion criteria - Offering intervention outside of trial setting
COMPASS: A Pilot Trial of an Early Palliative Care Intervention for Patients with End Stage Liver Disease ⁸⁶ United States NCT03022630 Feb 2017-Jun 2018 Single site	- Single-centre RCT 1-year follow-up - Intervention was inpatient PC consultation: general information about PC services and follow-up telephone calls with PC nurses. Control group received care as usual - Primary outcome: time to first hospital readmission	- Included patients with cirrhosis if their hepatologist answered “no” to “would you be surprised if this patient died within 1 year?” - Excluded if inability to consent (patient or surrogate), permission to enrol declined by hepatologist and prior transplant	400	Terminated due to slow recruitment. No protocol published	- Study published - N = 63 recruited - Intervention group lower readmission (HR 0.36, 95% CI 0.16-0.83, $p = 0.017$) and greater odds of having days alive outside hospital (OR 3.97, 95% CI 1.14-13.84, $p = 0.030$) vs. control group	Patients overwhelmed by hospitalisation so little appetite for research
Pilot Randomized Controlled Trial of an Advance Care Planning Video Decision Tool for Patients with Advanced Liver Disease ¹⁵⁰ United States NCT03557086 Sept 2018-Mar2020 Single site	- Single-centre RCT - Intervention: 5-minute video depicting three levels of care: life-prolonging (CPR/intubation) life-limiting (hospitalisation, no CPR/intubation, and comfort care. Controls: received verbal narrative of these goals of care - Primary outcome: feasibility (if at least 60% of eligible patients enrolled)	- Included transplant ineligible patients with cirrhosis and a score of ≥ 7 on the short portable mental status questionnaire - Excluded those receiving PC or with severe cognitive impairment	50	Completed. Protocol published as supplement to manuscript	- Manuscript published - Enrolled 50/89 (85%) of eligible participants 81% very comfortable watching the video - Intervention arm had higher mean knowledge scores vs. control arm (5.7 vs. 4.8; $p < 0.001$) and less likely to prefer to receive CPR (35% vs. 63%; $p = 0.09$)	

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Table 5. (continued)

Study/country/duration	Type of study, intervention and primary outcome	Inclusion/exclusion criteria	Sample size	Study status	Results	Barriers/facilitators
Randomised Clinical Trial: Palliative Long-term Abdominal Drains vs. Large Volume Paracentesis In Refractory Ascites Due to Cirrhosis (REDUCe Study) ¹⁸⁴ United Kingdom ISRCTN30697116 Sept 2015-Sept 2019 Five sites	• Multicentre feasibility RCT • Palliative LTAD vs. LVP 3 months follow-up • Primary outcome: As feasibility RCT no pre-defined outcomes. • Study success criteria: attrition not >50%, at least 80% uptake/completion of questionnaires/interviews and <10% LTAD removal due to complications	• Included patients with cirrhosis and refractory ascites, able to consent. • Excluded if eligible transplant/TIPS, loculated/chylous ascites, active infection and > grade 1 HE	48	Completed. Study protocol published	• Manuscript published • 36 recruited despite a year's extension (n = 19 LTAD, n = 17 LVP) • Study success criteria achieved • Only 2 LTAD patients admitted specifically for LVP • Median (IQR) fortnightly total ascites-related costs about 15% lower in LTAD group • Self-limiting cellulitis/leakage LTAD vs. LVP group 41% vs. 11% • Peritonitis incidence LTAD vs. LVP 6% vs. 11%	• Patients recruited late in disease trajectory • Hospital community interface created logistical issues • Underestimated time for site set up and over-estimated recruitment
Feasibility of a Palliative Care Intervention within Routine Care of Hepatocellular Carcinoma: A Pilot Randomized Controlled Trial ⁹⁵ United States	• Single-centre RCT • Patients with HCC offered outpatient PC • QoL and symptom burden assessed at 3 months using FACT-Hep and modified ESAS	• Included patients with cirrhosis and HCC • Excluded BCLC stage D	57	Completed. Manuscript published	• Post-intervention, symptom burden and QoL improved in the intervention arm and remained same or worsened in the control group.	
Benefits of Early Palliative Care Intervention in End Stage Liver Disease Patients Awaiting Liver Transplantation ⁴¹ American Jul 2013-May 2014	• Single-centre prospective cohort study • Early PC intervention: Nurse assessed and managed symptoms, PC needs, psychological and spiritual health • Symptom burden assessed using ESAS and depression using CES-D	• Included patients with cirrhosis and HCC	50	Completed. Manuscript published	• 50% of moderate-to-severe symptoms improved ($p < 0.05$), and 43% of patients showed improvement in clinically significant depressive symptoms ($p = 0.003$). • Patients with more symptoms showed greater improvement in CES-D ($p = 0.001$).	

CPR, cardiopulmonary resuscitation; ESLD, end-stage liver disease; HCC hepatocellular cancer; HE, hepatic encephalopathy; HR, hazard ratio; HRQoL, health-related quality of life; LTAD, long-term abdominal drain; LVP, large volume paracentesis; PC, palliative care; RCT, randomised controlled trial; SFLDQoL, short form liver disease quality of life; SPICT, supportive and palliative care indicators tool; TIPS, transjugular intrahepatic portosystemic shunt.

Heterogeneous cohort with unpredictable disease trajectory

Despite prognostic uncertainty in ACLD, repeated hospitalisations, the presence of refractory ascites, acute-on-chronic liver failure, frailty, and ongoing alcohol use portends a poor outcome.^{111,203} MORECare guidance on palliative research recommends recruiting individuals most likely to benefit.²⁰⁴ While recruiting those with a life expectancy of 3–6 months would be appropriate, this can be difficult, as patients with ACLD can rapidly deteriorate. This unpredictable disease trajectory, alongside screening failures, was a reason for low recruitment in the PETRA trial assessing palliative LTAD in refractory ascites²⁰⁵ (Table 5). Hepatologists may also be reluctant to consider palliative research due to curative options, such as liver transplantation (despite not being feasible for many with ACLD),⁶ as happened in the PETRA,²⁰⁵ and the Canadian trials assessing palliative LTADs²⁰⁶ (Table 5).

Recruitment challenges

Recruitment remains challenging in clinical trials, and a paucity of methodological precedent adds a further layer of complexity in palliative hepatology studies. About 75% of all clinical trials are terminated due to poor recruitment.²⁰⁷ “Lasagna law”²⁰⁸ states that “the number of participants actually available for recruitment in a study, usually turns out to be much lower than estimated in advance”. About 40% of palliative hepatology trials were prematurely terminated due to recruitment challenges (Table 5), the REDUCE study (assessing palliative LTADs in refractory ascites) only achieving two-thirds of its recruitment target (Table 5).¹⁸⁴

A pragmatic, multicentre RCT, with broad eligibility criteria facilitates recruitment, ensures a representative patient

population, and increases the real-life validity of results. Detailed pre-planned subgroup analysis can mitigate the effect of a heterogeneous population.⁷⁷ A feasibility study prior to the definitive trial can resolve recruitment and methodological issues, as shown by the REDUCE and the subsequent REDUCE2 studies^{184,185} (Table 5 and S4).

“Gate keeping”, the reluctance of HCPs to encourage palliative research because it is perceived as intrusive and burdensome, can hinder trial participation.²⁰⁹ However, evidence suggests such fears are unsubstantiated, as patients receiving PC and their caregivers frequently welcome opportunities for research participation.²¹⁰ Despite this, clinicians must appreciate a patient’s competing priorities. The COM-PASS trial⁸⁶ (Table 5) was prematurely terminated as patients felt overwhelmed by their recent hospitalisation with little appetite for research. Strategies to reduce participant burden include phone consultations, home visits, short patient-facing documents and proxy scores.

Offering palliative intervention outside of research settings, besides raising equipoise issues, can also negatively influence recruitment. However, this needs to be balanced by the fact that many palliative research participants may not be alive to see study results published. Restrictive inclusion criteria and offering the intervention outside of research settings negatively impacted recruitment both in the PETRA and Canadian trials assessing LTADs in refractory ascites^{205,206} (Table 5). Having early discussions on this issue with both funders and ethics committees can help frame helpful strategies.

Encouraging informal caregivers’ participation in research can aid recruitment, as they can potentially act as consultees in those with HE (see below) and also help deliver the

	Barriers	Facilitators
Disease trajectory and heterogeneity	• Unable to predict with certainty when palliative phase of illness has been reached • Lack of prognostic tools to accurately predict disease trajectory	• Use of surrogate markers for better prognostication such as recurrent hospitalisations due to decompensation, refractory ascites, frailty, and ongoing alcohol use • Use of SPICT, “surprise question” or Bristol prognostic score
Recruitment	• Restrictive inclusion criteria, ‘gatekeeping’ by researchers and caregivers • Inability to appreciate competing priorities and have palliative care discussions	• A feasibility study prior to main trial to resolve methodological issues • Pragmatic study design with broad inclusion criteria • Recruiting informal caregivers • Communication skills training for HCPs to include education on gatekeeping
Outcome measures and assessment tools	• Lack of appropriate outcomes and assessment tools for patients in palliative phase of ACLD	• Using patient-reported outcome measures including those focused on HRQoL and symptom load • Development of new disease-specific tools
Capacity and consent	• Disease-specific comorbidities such as encephalopathy which can result in patients being excluded from trials	• Early and clear discussions with funders and ethics committees to plan for patients losing capacity during the trial • The use of a consultee or independent medical advocates in the trial design
Missing data	• High attrition resulting in underpowered study, missing data which can affect results and introduce bias	• Work closely with trial statistician to factor attrition and missingness into sample size calculation • Clear strategy to deal with attrition and missing data when drafting the statistical analysis plan

Fig. 5. Barriers and facilitators for conducting palliative interventional trials in ACLD. ACLD, advanced chronic liver disease; HCPs, healthcare professionals; HRQoL, health-related quality of life; SPICT, supportive and palliative care indicators tool.

intervention (e.g. home drainage in those with LTADs).¹⁸⁵ A dyadic approach could also be adopted (i.e. recruiting patients and caregivers together),²¹¹ though researchers need to be cognisant of caregiver workload.¹⁸⁴

Finally, discussing palliative interventions can be emotive and challenging. Clearly communicating key study goals facilitates a trusting relationship with patients and their caregivers.²¹² However, many hepatology HCPs lack training to deliver this, underscoring the need for multidisciplinary teams, as well as communication skills training.^{213,214} In the feasibility REDUCe study¹⁸⁴ (Table 5), delayed PC discussions resulted in >50% of patients either not being recruited or dying within weeks of randomisation. Cognisant of this, in the follow-on definitive REDUCe2 study,¹⁸⁵ research staff have access to communication skills training (Table 5 and S4).

Lack of appropriate assessment tools and outcome measures

Many ACLD trials have objective primary outcomes, e.g. mortality, infection, and renal impairment, which are unsuitable for a palliative cohort. Patient or proxy-reported outcomes, such as HRQoL, and/or symptom burden, may be more appropriate outcomes. The chosen patient-reported outcome should ensure a feasible sample size and adequate power to detect a minimal clinically important difference, thus reducing sampling error.^{77,215} Though generic questionnaires are relevant to a wide range of patient groups, enabling aggregation and comparison across varied conditions and settings,²¹⁶ disease-specific tools offer greater sensitivity and specificity. While a number of validated questionnaires to assess HRQoL in compensated cirrhosis exist, the SFLDQoL (short form liver disease quality of life) questionnaire is the only validated tool in ACLD.²¹⁷ It predicts mortality with an equal, if not higher, accuracy than the MELD score²¹⁸ (Table 2).

HRQoL, though an appropriate primary outcome in palliative research, is not without its challenges. Firstly, though the SFLDQoL questionnaire is validated in ACLD, there is limited published data, and the minimal clinically important difference is unknown. Secondly, HRQoL is likely to decline over time in many patients with ACLD due to incurable disease. Thirdly, there is uncertainty regarding the optimal time point for measuring HRQoL; if assessed too early, research participants may have had inadequate experience of the intervention, but if assessed too late, patients may have deteriorated, resulting in missing data.⁷⁷

Similar challenges apply to the assessment of symptom burden, though a tool to assess ascites symptoms in ACLD has been recently validated²¹⁹ (Table 2).

Capacity and consent issues

A unique challenge in patients with ACLD is HE, which can occur unexpectedly and fluctuate. Though those with HE are amongst the most vulnerable of patients with ACLD, often with poor HRQoL,^{220,221} they are often excluded from clinical trials due to capacity issues. As per the UK Mental Capacity Act 2005,²²² patients lacking capacity can be included if equal effectiveness research cannot be conducted by excluding them.²²² Patients with HE should therefore not be excluded from research, as they are representative of the group under investigation.⁷⁷ To circumvent issues around consent, a consultee (informal caregiver or HCP who is independent from the

research), or an independent medical capacity advocate can be pre-appointed to determine if research participation is in the patient's best interest.⁷⁷ Earlier palliative hepatology studies excluded patients with HE, which may have contributed to poor recruitment.^{205,206} The REDUCe2 trial, investigating palliative LTADs in refractory ascites, while excluding those with HE at onset, is recruiting consultees to act on participants' behalf should they lose capacity during the trial.¹⁸⁵ The Chelsea II trial, assessing if clinically assisted hydration at EoL prevents delirium, is also enrolling consultees.²²³

Dealing with missing data

A systematic review of palliative trials showed that on average about 25% of primary outcome data were missing,²²⁴ compared with <10% in non-palliative studies.²²⁵ Missing data can reduce the ability of a study to determine if the intervention is effective, affect the validity of the findings, and introduce bias.²²⁶ MOREcare and Marie Curie guidance on dealing with attrition and handling/reporting missing data recommend reporting attrition as due to death, withdrawal/disease progression, or at random.^{204,226} Attrition should be factored into sample size calculations to ensure that the study is adequately powered.

Data may be missing completely at random, at random, or not at random.²²⁵ Strategies to reduce missing data include collecting the minimum amount of data over the shortest possible duration, incentivising participants to return their data, using proxy data, collecting auxiliary variables expected to predict missing data, and training staff on the importance of missing data.⁷⁷ Nevertheless, the use of proxy data is controversial, as studies have found that proxy ratings can be equivalent to, underestimate, or overestimate patient-reported scores.^{227,228} Strategies to handle missing data include multiple imputations,²²⁹ inverse probability weighting, model-based approaches,²²⁶ repeated measurements of primary outcome data⁷⁷, and terminal decline joint modelling.²³⁰

Do recent and ongoing trials support early integration of PC in ACLD?

There has recently been an increase in well-designed palliative interventional studies, including RCTs, which are summarised in Table 5 and S3. Interventions have varied from provision of early generalist and specialist PC, ACP, and palliative LTADs for refractory ascites. Results show improvements in symptom burden, HRQoL, and depressive symptoms; lower hospital readmission rates with admissions being more patient-centred; greater odds of being alive outside of hospital; higher knowledge scores regarding ACP; lower preference for CPR; and increased transfer of care to the community, with reduced healthcare resource utilisation (Table 5). Qualitative data show that palliative interventions have high acceptability among patients and caregivers. Though hepatologists find PC training time consuming, it improved their knowledge and confidence in undertaking difficult conversations (Table S3).

Summary statement

There are multiple barriers to the conduct of palliative interventional trials in hepatology, including a heterogeneous cohort with an unpredictable disease trajectory, recruitment

challenges, lack of appropriate assessment tools and outcome measures, capacity and consent issues, and attrition. Strategies to overcome these issues include an initial feasibility study to resolve methodological issues, pragmatic study design with broad inclusion criteria, addressing gatekeeping, and having a clear statistical plan to deal with missing data. In a palliative cohort, patient-reported outcomes may be the most appropriate outcome measure. Mixed-methods research is particularly relevant in this group.

Recommendations

- Patients with ACLD and their informal caregivers should be encouraged to participate in palliative hepatology RCTs.
- Patient-reported outcomes should be the most appropriate primary outcome in a palliative hepatology cohort.
- When designing and conducting palliative hepatology studies, there should be a clear strategy to address recruitment challenges, consent issues, attrition and missing data. A feasibility study could help address methodological issues.
- Funders should prioritise palliative hepatology research to address historical inequity in this area.

Conclusions and future directions

Patients with ACLD have complex symptoms that impact their HRQoL and result in caregiver distress. Most patients with ACLD will not receive a liver transplant, yet are only offered PC in the last few days or weeks of life. Having discussions around prognosis, including ACP, allows for timely (and hence better

Box 1. Areas in palliative hepatology that need addressing in the future.

- Training medical students, gastroenterology and hepatology trainees, hepatologists and nurses in generalist palliative care and advance care planning. Provide communication skills training if necessary.
- To establish standardised and clinically validated palliative care consultation criteria including optimal timing, populations to reach and which elements of palliative care are most critical and when.
- Development and validation of tools to assess health-related quality of life and symptom burden in advanced chronic liver disease.
- Investment by stakeholders including funders to support palliative hepatology research.
- Development of palliative specialist interest groups within liver societies and increased focus on palliative care in societal guidelines as well as palliative hepatology sessions at annual meetings.
- Establishing metrics for quality of palliative care in advanced chronic liver disease.

quality) delivery of PC which can be offered in parallel to curative options, including liver transplant. PC needs to be embedded within hepatology services as it enables symptom control and improves HRQoL for both patients and their caregivers. PC is best delivered by multidisciplinary/multi-professional teams. Recent society guidelines,^{8,9} including this position paper, highlight the importance of PC in ACLD. We hope this paves the way for high-quality palliative research/evidenced-based interventions, thereby addressing the current inequity in PC provision for this vulnerable and disenfranchised cohort. Areas that need addressing in the future are summarised in [Box 1](#).

Affiliations

¹Department of Clinical and Experimental Medicine, Brighton & Sussex Medical School, University of Brighton and University of Sussex, Brighton, UK; ²Department of Gastroenterology and Hepatology (Digestive Diseases), University Hospitals Sussex NHS Foundation Trust, Royal Sussex County Hospital, Brighton, UK; ³Division of Gastroenterology & Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria; ⁴Department of Nursing and Therapeutic Services, Hoch Health Ostschweiz Cantonal Hospital St.Gallen, St.Gallen, Switzerland; ⁵Institute of Nursing Science, Department Public Health, Faculty of Medicine, University of Basel, Switzerland; ⁶Gastro Unit, Copenhagen University Hospital Hvidovre, Hvidovre and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; ⁷Amsterdam UMC, Department of Gastroenterology and Hepatology, Amsterdam, The Netherlands; ⁸Faculty of Medicine of the University of Porto, Portugal; ⁹Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; ¹⁰Center for Digestive Diseases and Liver Transplant, Fundeni Clinical Institute, Bucharest, Romania; ¹¹Center of Excellence in Translational Medicine, Fundeni Clinical Institute, Bucharest, Romania; ¹²Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, London, UK; ¹³Department of Palliative care, Institute of Live Studies, Kings College Hospital NHS Foundation Trust, London, UK; ¹⁴Department of Gastroenterology and Hepatology, Royal Devon University Healthcare NHS Foundation Trust, Devon, UK

Abbreviations

ACP, advance care planning; ACLD, advanced chronic liver disease; ALD, alcohol-related liver disease; BCLC, Barcelona Clinic Liver Cancer; CPR, cardiopulmonary resuscitation; CTP, Child-Turcotte-Pugh; EASL, European Association for the Study of the Liver; EoL, end of life; EoLC, end-of-life care; HCP, healthcare professional; HRQoL, health-related quality of life; HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; LVP, large volume paracentesis; LTAD, long-term abdominal drains; MELD, model for end-stage liver disease; MDT, multidisciplinary team; PC, palliative care; PRO, patient-reported outcomes; PBC, primary biliary cholangitis; RCT, randomised controlled trial; SQ, surprise question; WHO, World Health Organization.

Financial support

No financial support was received to produce this manuscript.

Conflicts of interest

SV research grants and consultancy Gilead Sciences (IN-UK-337-1981; IN-UK-987-5337); Rocket Medical and Becton Dickinson provided LTAD free of cost for REDUCe and REDUCe2 studies. MP speaker honoraria from AstraZeneca, Bayer, BMS, Eisai, Ipsen, Lilly, MSD, Roche; consultant/advisory board for AstraZeneca, Bayer, BMS, Eisai, Ipsen, Lilly, MSD, Roche; grants from AstraZeneca, Bayer, BMS, Eisai, Roche. PKH speaker honoraria from Merz; consultant/advisory board member for Abbvie and Gilead Sciences. LLG speaker honoraria from AstraZeneca, Novo Nordisk, Sobi, BD, Ipsen; consultant/advisory board member for AstraZeneca, Novo Nordisk, BD, Boehringer Ingelheim; grants from Novo Nordisk, Sobi International, Alexion; travel support from Ipsen. RBT Grants from the Netherlands Organisation for Health Research and Development (ZonMw), Vaillant Foundation; speaker fee WL Gore, Ipsen; Advisory board: ProQR. LG Research grants from Gilead; speaker honoraria from Gilead, AstraZeneca, AbbVie, Eli Lilly, Novo Nordisk, Sanofi, Alfa Sigma, Roche. None: LM, RN, WP, BH.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

SV chaired the position paper. Section 1 WP, LLG, PKH; section 2 LM, SV; section 3 MP, BT, BH; section 4 RN, LG, SV, BH; section 5 PKH, LLG; section 6 BH; section 7 SV, LLG. All authors reviewed and approved the final draft of the manuscript.

Acknowledgements

We are grateful to Mrs. Joan Bedlington and Ms. Shani Steer (Patient and Public Involvement group) for their review and comments and to Dr Yazan Haddadin for producing the figures (created using Biorender). Finally, we thank Ms. Katerina Katsarou, EASL Scientific Programme Coordinator for providing logistical support.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2025.101686>.

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Received 21 November 2025; accepted 21 November 2025; Available online 3 March 2026