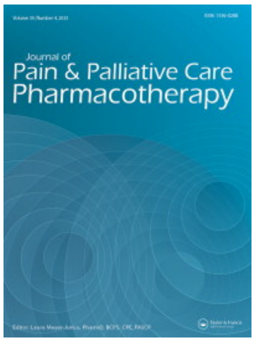

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REVIEW ARTICLE

Early Palliative Care Integration in End-Stage Liver Disease: A Narrative Review of Clinical Strategies for Symptom Control and Quality of Life

Daniela Sarria-Gómez[a,b], Cristhian Camilo Martínez Torres[c], Diana Estrada-Bermúdez[d] and Liliana Saavedra[d]

[a]Universidad de La Sabana. Chía, Cundinamarca, Colombia; [b]Unidad de Dolor y Cuidados Paliativos, Instituto Nacional de Cancerología, Bogotá, Colombia; [c]Universidad El Bosque, Bogotá, Colombia; [d]Servicio de Cuidados Paliativos, Hospital Militar Central, Bogotá, Colombia

ABSTRACT

End-stage liver disease (ESLD) is associated with a high symptom burden, poor prognosis, and limited access to curative disease. Despite growing evidence supporting the role of palliative care (PC), its integration into the routine management of ESLD remains limited and inconsistent. To synthesize the current evidence on the role of palliative care in ESLD, emphasizing its impact on quality of life and including strategies for symptom control and effective clinical integration. A narrative review with a systematic approach was conducted. PubMed, Scopus, Embase, and SciELO were searched for English- and Spanish-language studies published between 2015 and 2025. Studies were selected based on methodological rigor and relevance to PC interventions in ESLD. Key barriers to PC implementation include misconceptions about its use being limited to terminal phases, lack of referral criteria, and insufficient coordination between specialties. Evidence shows that early PC involvement improves symptom control (pain, dyspnea, pruritus, encephalopathy), decreases avoidable hospitalizations, and facilitates shared decision-making. Early and structured integration of palliative care into ESLD management is essential. Health systems should prioritize interdisciplinary care models, establish clear referral criteria, and promote a care approach focused on patient well-being, autonomy, and dignity.

HIGHLIGHTS

- Early Palliative Care (PC) improves outcomes in end-stage liver disease (ESLD).
- Integration of PC reduces hospitalizations and enhances quality of life.
- Symptom control in ESLD remains underprioritized and poorly standardized.
- Referral criteria for PC in ESLD are lacking despite clear clinical indicators.
- A narrative synthesis highlights PC as essential in advanced liver care.

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Palliative care; end-stage liver disease; chronic liver failure; end-of-life care; hepatic encephalopathy; ascites; dyspnea; quality of life

Introduction

End-stage liver disease (ESLD) is a major contributor to global morbidity and mortality. Patients with decompensated cirrhosis typically survive a median of 2 years, facing a substantial symptom burden and frequent hospitalizations due to complications such as ascites, hepatic encephalopathy, gastrointestinal bleeding, and hepatorenal syndrome (1). Despite the poor prognosis, palliative care (PC) remains underutilized, often initiated only in advanced stages or after patients are removed from the liver transplant waiting list (1,2).

Consistent with the World Health Organization, palliative care is an approach that enhances the quality of life of adults and children with life-threatening illness and their families by preventing and relieving suffering through early identification, appropriate assessment, and treatment of pain and other physical, psychosocial, and spiritual problems (3). This care model is not limited to end-of-life interventions but rather emphasizes holistic support throughout the disease trajectory. Understanding this comprehensive scope is essential to address misconceptions and promote timely integration in the context of end-stage liver disease (4).

This holistic approach requires collaboration between specialists, who bring complementary expertise to patient management. While hepatologists and internists focus on disease-directed

CONTACT Daniela Sarria-Gómez dsarriag@gmail.com Unidad de Dolor y Cuidados Paliativos, Instituto Nacional de Cancerología, Bogotá, Colombia.

interventions, palliative care teams address symptom burden and quality of life across the illness trajectory (4).

Liver transplantation is the only curative option for ESLD. However, access is limited by strict eligibility criteria, organ scarcity, and comorbid conditions (5). In this context, palliative care serves as a critical approach to enhancing quality of life by relieving physical symptoms, supporting emotional well-being, addressing psychosocial needs, and guiding end-of-life decision-making within a holistic framework that also facilitates advance care planning (6). Early PC integration has shown substantial benefits in patients with ESLD, evidence suggests that it can reduce avoidable hospitalizations, enhance resource efficiency, and improve overall patient and caregiver experience (7).

The symptom burden in ESLD closely mirrors that of advanced cancer, yet PC is less frequently incorporated into routine management for these patients (2). Barriers include misconceptions that PC is appropriate only in terminal phases, uncertainty around disease trajectory, and the absence of standardized referral criteria (8). However, recent evidence demonstrates that early PC involvement improves symptom control, lowers hospital utilization, and increases alignment with patient care preferences (9). This review aims to synthesize current evidence on the role of PC in advanced liver disease, focusing on its effects on quality of life and approaches to clinical integration.

Methods

A narrative review was conducted, incorporating systematic elements to enhance methodological transparency. These included structured search strategies and predefined inclusion and exclusion criteria. While not a systematic review, the methodology was informed by best practices outlined in the Cochrane Handbook and selected components of the PRISMA framework to support clarity and consistency in the literature selection process.

The literature search was conducted across major biomedical databases, including PubMed/MEDLINE, Scopus, Embase, and SciELO. Studies published between January 2015 and April 2025 were considered. This period was selected to compile the most current and clinically relevant literature. Furthermore, research on the early integration of palliative care in liver disease has significantly increased over the past decade, making it a methodologically appropriate starting point MeSH terms and targeted keywords were combined using Boolean operators, such as "Palliative Care" AND "Liver Diseases", "End-Stage Liver Disease" AND "Supportive Care", and "Cirrhosis" AND "Symptom Management" AND "Palliative Care". Filters were applied to include English- and Spanish-language studies, human subjects, and peer-reviewed publications.

Eligible studies included clinical trials, cohort studies, systematic and narrative reviews, as well as meta-analyses evaluating the impact of PC on patients with advanced liver disease. Articles that described specific palliative interventions and symptom management strategies were also included. Studies were excluded if they focused solely on liver transplantation, involved pediatric populations, or lacked transparent methodology—defined as the absence of key information such as inclusion and exclusion criteria, data sources, or a clear description of palliative care interventions.

The selection process occurred in three phases. First, titles and abstracts were screened to remove studies not meeting the inclusion criteria. Then, the full texts of potentially eligible studies were assessed to determine their relevance. In cases where studies partially met the criteria or presented uncertainty regarding their applicability, priority was given to those providing clear descriptions of palliative interventions, patient outcomes, or clinical relevance to advanced liver disease. This approach aimed to ensure the inclusion of studies with the greatest potential to support the objectives of the review.

Methodological quality was assessed using tools specific to each study type. For randomized controlled trials, the Cochrane Risk of Bias Tool (RoB 2) was applied (10); for observational studies, the Newcastle-Ottawa Scale was used (11). In addition, the PRISMA checklist was employed to evaluate the reporting quality of included systematic reviews. Only studies rated as having moderate to high methodological quality were considered. A standardized data extraction table was developed exclusively for primary research studies, to facilitate comparative analysis and narrative synthesis. It summarizes the study design, population, intervention, and reported outcomes (see Table 1).

Results

ESLD is a major global contributor to morbidity and mortality. In countries such as the United States and the United Kingdom, liver-related mortality has risen significantly over the past few decades (2). In the United States, it was estimated that in 2008 approximately 5.5 million individuals were living with decompensated liver disease, accounting for around 500,000 hospitalizations and 40,000 deaths annually (5). More recent data from the Centers for Disease Control and Prevention (CDC) report 52,222 deaths from chronic liver disease and cirrhosis in 2023, corresponding to a mortality rate of 15.6 per 100,000 population, ranking as the ninth leading cause of death in the United States (24). In Europe, Portugal reports the highest mortality rate from hepatocellular carcinoma (1).

Excessive alcohol use, chronic viral hepatitis, and metabolic dysfunction-associated steatotic liver disease (MASLD) are the most common causes of ESLD. The prevalence of MASLD continues to grow, largely due to increasing rates of obesity and metabolic syndrome (25). By 2030, MASLD is expected to become the leading indication for liver transplantation (25).

Patients with decompensated cirrhosis have a median survival of about 2 years, which further decreases in the presence of complications such as refractory ascites, recurrent hepatic encephalopathy, or hepatorenal syndrome (12). Despite this high mortality, only a small proportion of patients receive timely palliative care. In Portugal, less than 8% of

Table 1. Characteristics of primary research studies included in the review.

Ref	Authors	Year	Country	Study design	Population (sample size)	Intervention/study focus	Reported outcomes
(1)	Oliveira et al.	2024	Portugal	Cohort analysis	312 ESLD patients	Palliative care use and referral factors	Low palliative care referral rates; factors associated with referral included disease severity
(6)	Patel et al.	2020	USA	Observational study	1,022 ESLD patients	Quality assessment of palliative care	Identified gaps in palliative care quality; need for standardized measures
(8)	Sohal et al.	2024	USA	National retrospective analysis	1,203,420 decompensated cirrhosis patients (2016–2020)	Trends in palliative care utilization	Increased palliative care use over time, but still underutilized in ESLD
(12)	Baumann et al.	2015	USA	Prospective cohort	50 ESLD patients awaiting transplant	Early palliative care intervention	Improved symptom burden and quality of life with early palliative care
(13).	Peng et al.	2019	UK	Meta-analysis	42 studies (6,747 ESLD patients)	Symptom prevalence and QoL	High symptom burden (fatigue, pain, depression); poor QoL in ESLD
(14)	Ufere et al.	2019	USA	Retrospective cohort	374 ESLD patients	Barriers to palliative care and advance care planning	Low rates of palliative care discussions; barriers included prognostic uncertainty
(15)	Shehadah et al.	2024	USA	Retrospective analysis	120 ESLD patients (non-transplant)	Early palliative care referral	Improved end-of-life care with early palliative care referral
(16)	Brown et al.	2021	USA	Retrospective cohort	348 decompensated cirrhosis patients	MELD-Na score for 6-month mortality prediction	MELD-Na accurately predicts mortality; potential trigger for hospice referral
(17)	Barosa et al.	2017	Portugal	Observational study	98 ACLF patients	Comparison of mortality scores (CLIF-C ACLF, MELD, MELD-Na, CTP)	CLIF-C ACLF score outperformed MELD/ MELD-Na in mortality prediction
(18)	Hoilat et al.	2021	USA	Meta-analysis	7 studies ($N=524$ patients)	PEG vs. lactulose for hepatic encephalopathy	PEG was more effective than lactulose in improving HE
(19)	Rich et al.	2022	USA	Retrospective cohort	1,053 HCC patients	Association between cachexia and prognosis	Cachexia prevalent in HCC and linked to worse survival
(20)	Hansen et al.	2015	USA	Cross-sectional study	50 ESLD patients near end-of-life	Symptom distress assessment	High symptom distress (pain, fatigue, anxiety) in ESLD patients
(21)	Holden et al.	2020	USA	Retrospective cohort	1,186 decompensated cirrhosis patients	Factors influencing palliative care/hospice referral	Low referral rates, factors included comorbidities, social support, and clinician communication
(22)	Woodland et al.	2023	UK	National cohort study	21,953 chronic liver disease patients	Equity in end-of-life care access	Significant inequities in palliative care access for liver disease vs. other conditions
(23)	Donlan et al.	2021	USA	Qualitative study	20 ESLD patients + 12 caregivers	Perspectives on palliative care	Patients/caregivers valued palliative care but faced communication and timing barriers

Abbreviations: ACLF Acute-on-Chronic Liver Failure, CLIF-C ACLF Chronic Liver Failure Consortium ACLF score, CTP Child-Turcotte-Pugh, ESLD End-Stage Liver Disease, HE Hepatic Encephalopathy, HCC Hepatocellular Carcinoma, MELD Model for End-Stage Liver Disease, MELD-Na MELD-Sodium, PEG Polyethylene Glycol, QoL Quality of Life.

patients with ESLD are referred to palliative services, often during the final stages of illness (1).

Pathophysiology

ESLD is a progressive illness that develops after inflammatory changes in the liver lead to fibrosis and disruption of liver structure and function. The only existing cure is liver transplantation, an option available to only a minority of patients. Remaining therapies are palliative in nature (26). ESLD marks the terminal phase of cirrhosis. The disease course is generally divided into two phases: compensated and decompensated cirrhosis (9).

In compensated cirrhosis, the liver maintains partial function, allowing patients to live longer with fewer symptoms. However, ongoing fibrosis and rising portal pressure increase the risk of decompensation (27). Decompensated cirrhosis presents with life-threatening complications, including ascites, hepatic encephalopathy, variceal gastrointestinal bleeding, and hepatorenal syndrome; however, with appropriate treatment, some patients may recover sufficient liver function to return to a compensated state. (see Table 2).

Table 2. Description of life-threatening complications of decompensated cirrhosis.

Complication	Description
Ascites	Ascites is the most frequent complication in decompensated cirrhosis, associated with a 50% 2-year mortality rate (2). Fluid accumulation in the peritoneal cavity causes discomfort, including pain and dyspnea, and increases the risk of infections such as spontaneous bacterial peritonitis (SBP), which can be fatal (28). Refractory ascites remains difficult to manage and often requires repeated paracentesis or long-term abdominal drains for symptom relief (29).
Hepatic Encephalopathy	Hepatic encephalopathy results from the buildup of neurotoxic substances like ammonia in the brain. It impairs cognitive function, reduces quality of life, and increases the risk of death (13). Recurrent episodes are associated with particularly poor prognosis and significantly lower survival rates (30).
Variceal Gastrointestinal Bleeding	Caused by severe portal hypertension, variceal bleeding is a life-threatening complication with a high recurrence rate. Despite advances in endoscopic and pharmacologic therapies, it remains a major contributor to morbidity and mortality in decompensated cirrhosis (31).
Hepatorenal Syndrome (HRS)	HRS represents advanced circulatory dysfunction and manifests as progressive renal failure in the absence of alternative causes of kidney injury. It carries a poor prognosis, with an 80% 3-month mortality rate if untreated (14).

Prognosis

The prognosis of ESLD is closely linked to the degree of decompensation; while early stages may allow for recompensation with appropriate management, advanced decompensation—particularly in acute-on-chronic liver failure (ACLF)—is associated with poor resuscitation outcomes and high short-term mortality (32,33). Patients with decompensated cirrhosis have a poor prognosis, with cumulative mortality reaching approximately 30% at 1 year and increasing thereafter; in contrast, ACLF is characterized by high short-term mortality—commonly 30–70% within 1–3 months—reflecting the impact of multiorgan dysfunction/failure (34). Patients with ACLF often require a multidisciplinary approach that includes intensive care and, in select cases, liver transplantation (35).

Portal hypertension and circulatory dysfunction in cirrhosis contribute to a proinflammatory and prothrombotic state, increasing the risk of complications such as portal vein thrombosis and sepsis (29). When combined with malnutrition and sarcopenia—common in this population—prognosis worsens significantly (30,36).

Predictive tools

Prognosis in ESLD varies widely and depends on multiple clinical factors. Several validated tools help estimate survival and guide decision-making. Table 3 summarizes the most widely used prognostic models.

Palliative Performance Score (PPS) (39) is a well-established tool in palliative care for evaluating functional status. The PPS has five functional dimensions: ambulation, activity level and evidence of disease, self-care, oral intake, and level of consciousness. A decline in PPS is associated with worsening MELD scores, highlighting its potential as a complementary indicator of mortality risk, even in patients without underlying hepatic malignancies.

Early integration of palliative care

Despite the substantial symptom burden and high morbidity associated with ESLD, the integration of PC remains limited. Barriers include patient and provider misconceptions about the role of PC—particularly among liver transplantation candidates—as well as inadequate provider training and

Table 3. Summary of prognostic tools in advanced liver disease.

Tool	Description
MELD (Model for End-Stage Liver Disease) (16)	• It is a reliable predictor of 3-month survival in patients with cirrhosis of any etiology. • Incorporates bilirubin, creatinine, INR. • The MELD score has demonstrated greater accuracy than the Child-Turcotte-Pugh (CTP) score in predicting 3-month mortality.
MELD-Na (16)	• Predicts short- and medium-term mortality in cirrhosis. A score >29 is associated with a 90-day mortality of 53%. • It includes the MELD parameters, with the addition of serum sodium. • An increase of >5 points within 30 days triples mortality risk. • Most predictive during the first year of follow-up.
CLIF-C ACLF (Chronic Liver Failure Consortium for Acute-on-Chronic Liver Failure) (17)	• More accurate than MELD for predicting 28- and 90-day mortality in ACLF patients. • ACLF grades 2 or 3 warrant referral to palliative care.
Child-Turcotte-Pugh (CTP) Class C (9)	• Based on bilirubin, albumin, INR, ascites, and hepatic encephalopathy. • Class C (score ≥10) corresponds to a 45% 1-year survival rate. • Scores of 14–15 typically indicate advanced ESLD.
ECOG (Eastern Cooperative Oncology Group) (37)	• Originally validated in oncology to assess functional status. • In advanced liver disease, ECOG ≥3 reflects severe functional impairment (limited self-care or confined to bed/chair >50% of the day). • Not liver-specific but used in ESLD and transplant settings (especially hepatocellular carcinoma) to identify poor prognosis and support early palliative care referral.
Frailty Index (38) Fried frailty index	• Serves as a prognostic indicator independent of liver disease scores. • Each 1-point increase in frailty is associated with a 50% higher mortality risk. • High frailty may justify early PC referral, even in the absence of severe biochemical abnormalities.

reimbursement challenges (36). Furthermore, insufficient incorporation of palliative care principles into hepatology and transplant teams, the absence of standardized referral pathways, and variability in service availability across institutions and regions exacerbate inequities in access (14,40). The persistent stigma surrounding palliative care, often perceived as synonymous with end-of-life care, further hinders its timely utilization in this patient population. Addressing these multi-level obstacles is essential to promote earlier and more effective integration of palliative care in advanced liver disease.

Referral to palliative care

PC should be integrated early and in parallel with standard medical therapy, especially for patients with decompensated cirrhosis or those ineligible for liver transplantation (41). Referral to PC is recommended in the following clinical scenarios (9):

- Persistent ACLF grade 2–3 beyond 3–7 days of hospitalization, or CLIF-C ACLF score >70 at day 3 of ICU admission, suggesting futility of intensive care support (42).
- Child-Pugh Class C with two or more hospital admissions within 6 months.
- ECOG performance status 3–4 (i.e., limited self-care or total dependence, with the patient confined to bed or chair most of the day) with associated sarcopenia (43). ECOG should only be utilized for patients with ESLD secondary to hepatocellular carcinoma or liver metastases.
- Non-transplant candidates with limited life expectancy and a high symptom burden.
- Patients who are liver transplant candidates but present ongoing high risk of mortality (e.g., high wait-list mortality in ACLF).
- Complex psychosocial situations, including high caregiver burden or conflicts regarding goals of care (42).
- MELD ≥ 20.

In clinical practice, hepatologists often lack clear, actionable criteria for timely palliative care referral. To support implementation, we propose a simplified hospital-based referral algorithm based on key prognostic indicators such as MELD, CLIF-C ACLF, functional status, and transplant eligibility. This algorithm facilitates early integration of palliative care into hepatology workflows and promotes a patient-centered approach throughout the disease trajectory (see Figure 1).

Palliative symptom management in end-stage liver disease

Advanced liver disease is associated with multiple symptoms that severely impact quality of life. Palliative care focuses on managing these symptoms to improve comfort and well-being (35,41). The following are evidence-based strategies for managing the most frequent symptoms.

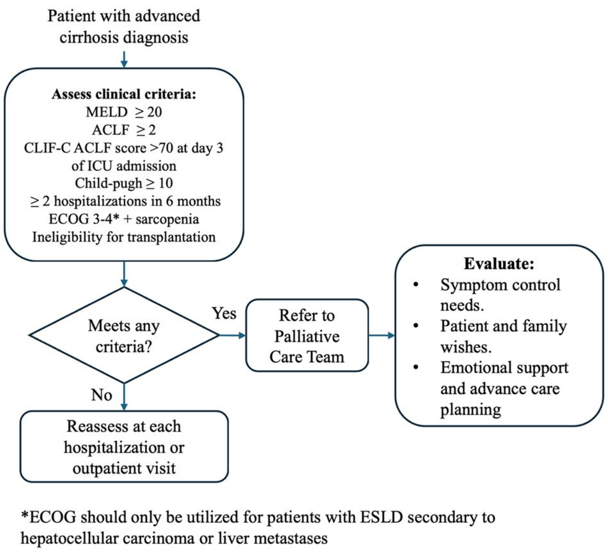

Figure 1. Hospital-based referral algorithm for palliative care integration in end-stage liver disease.

Pain

Pain management in cirrhosis is complex due to altered drug metabolism, changes in protein binding, and increased risks of hepatotoxicity, renal impairment, and hepatic encephalopathy (44–46). Given that the liver is the principal organ for drug metabolism, ESLD profoundly alters pharmacokinetics and pharmacodynamics. In ESLD, phase I metabolism via cytochrome P450 (CYP450) enzymes is typically impaired early, leading to reduced hepatic clearance and elevated serum drug concentrations. In contrast, phase II metabolism through glucuronidation is preserved for a longer period of time in cirrhosis (47). Furthermore, progressive reductions in hepatic blood flow characteristic of advanced disease can exacerbate these effects. Such alterations underscore the importance of carefully selecting and adjusting medications to minimize toxicity and optimize therapeutic outcomes (48).

Beyond pharmacological considerations, a multimodal approach to pain is encouraged. Advanced liver diseases and cirrhosis are often associated with multiple medical and psychological comorbidities, as well as socio-economic factors, all of which significantly influence pain perception, tolerance, and modulation. Therefore, addressing these aspects constitutes a vital adjunct to analgesic therapy. Nonpharmacologic strategies such as physiotherapy, cognitive-behavioral therapy (CBT), relaxation techniques, acupuncture, spinal manipulation, and traditional practices like massage, yoga, qigong, and ayurveda may offer benefit. Additionally, emerging modalities including transcutaneous electrical nerve stimulation, low-level laser therapy, digital applications, and structured multimodal pain programs should be considered in this patient population (49).

Treatment should balance effective pain control with patient safety, avoiding further liver injury. The strategies below reflect current evidence.

Pain assessment should begin with identifying the pain type and etiology—nociceptive, nociplastic, neuropathic, or mixed—and tailoring treatment accordingly (50). In cirrhosis, pain can arise from various causes and locations:

- Abdominal pain may result from distension, ascites, spontaneous bacterial peritonitis (SBP), neuropathic dysfunction, or splenomegaly.
- Lower back pain often reflects osteoporosis, immobility, fractures, or massive ascites, and may also be linked to metastatic liver cancer (13).
- Generalized pain may stem from chronic systemic inflammation.
- In hepatobiliary malignancies, pain may result from tumor burden, capsule distension, visceral involvement, or gastric compression (51).

A stepwise approach is recommended, starting with the safest agents and escalating only when necessary. Initiate treatment at low doses, extend dosing intervals, and avoid drugs with extensive hepatic metabolism or toxic metabolites. Monitoring liver, renal, and neurological function is essential (52). The following recommendations are for nociceptive pain:

First-line treatment: acetaminophen (paracetamol). Acetaminophen is the preferred agent for mild to moderate pain in cirrhosis. It undergoes glucuronidation and sulfation, forming nontoxic metabolites. For acute pain, doses up to 3 g/day may be acceptable for short durations (<14 days), while for chronic use, the dose should be limited to 2 g/day. It should be noted that these recommended cutoffs are based primarily on expert opinion, as pharmacokinetic studies in cirrhosis have not demonstrated a need for mandatory dose adjustment according to FDA criteria (53). Alcohol consumption should be strictly avoided due to increased risk of hepatotoxicity (46). Despite concerns, hepatotoxicity is rare when dosed appropriately and in the absence of chronic alcohol use (50). Unlike NSAIDs, acetaminophen does not substantially increase the risk of gastrointestinal bleeding (13), nor does it promote fluid retention, but evidence suggests it may still carry a potential risk of renal impairment, especially with long-term or high-dose use (54).

Second-line treatment: corticosteroids and topical agents. If acetaminophen is insufficient, topical diclofenac gel may be used selectively with close supervision (51). Corticosteroids have been shown to be effective in the management of cancer-related pain in patients with ESLD, particularly for hepatic capsular distension and pain secondary to bone metastases. Among them, dexamethasone 8 mg/day is often preferred due to its minimal mineralocorticoid activity, which reduces the risk of fluid retention and related complications (55).

Third-line treatment: opioids and NSAIDs. When pain remains uncontrolled despite non-opioid measures, carefully selected short-acting opioids may be considered, always at the lowest effective dose and under close monitoring (52).

Hydromorphone at low doses is one potential option, as it undergoes glucuronidation, a pathway relatively preserved in cirrhosis compared with phase I metabolism via CYP450 enzymes and is available in short-acting formulations. Buprenorphine may also be considered given its partial mu-opioid receptor agonism and pharmacokinetic profile (56), while reduced-dose oxycodone can be used with caution due to its reliance on CYP450 metabolism (50). Although intravenous fentanyl has a favorable metabolic profile in cirrhosis, its outpatient use is limited by the lack of suitable short-acting formulations and the risks associated with transdermal patches, including dose stacking and contraindications in cachectic patients (31).

Morphine clearance is significantly reduced in cirrhotic patients, necessitating lower and less frequent dosing to avoid toxicity, particularly in those with concurrent renal impairment. Hydrocodone and codeine should be avoided, as their CYP450-dependent metabolism may result in unpredictable and inadequate analgesia due to impaired conversion to active metabolites (55). Avoid tramadol and tapentadol, especially in patients taking serotonergic antidepressants (13). Methadone may be considered in selected cases of refractory pain or significant renal impairment; however, in advanced liver disease (Child-Pugh Class C) it must be used with extreme caution because of impaired metabolism and increased free drug availability, with recommendations for lower starting doses and extended titration intervals of 10–14 days to minimize toxicity (57). Importantly, all opioids may exacerbate hepatic encephalopathy and contribute to constipation, sedation, and respiratory depression (51). Therefore, opioid use in ESLD should always be individualized, started at the lowest effective dose, and closely monitored.

Nonselective NSAIDs, such as ibuprofen and naproxen, are contraindicated due to renal toxicity and bleeding risk (45). Selective COX-2 inhibitors, like celecoxib, may be used with caution in patients with Child-Pugh A or B cirrhosis, at reduced doses and for ≤5 days, under close medical supervision (46).

In patients with ESLD who present with neuropathic pain, adjuvant agents may be considered (45): Gabapentin and pregabalin are undergo minimal hepatic metabolism, though dose adjustment is needed in renal impairment (52). Gabapentin usually starts at 100–300 mg/day and can be titrated gradually, up to 2400 mg/day as tolerated, to avoid sedation or dizziness. Pregabalin may be initiated at 50–100 mg/day, with slow titration up to 600 mg/day (46). When considering tricyclic antidepressants, nortriptyline 10 mg/day and desipramine 12,5 mg/day are generally preferred over amitriptyline and imipramine in patients with advanced liver disease, as they are associated with reduced sedative effects. Avoid venlafaxine and duloxetine due to concerns about hepatotoxicity (52). Topical options for neuropathic pain include lidocaine patches, which are effective and safe due to low systemic absorption. Figure 2 summarizes the analgesic management approach.

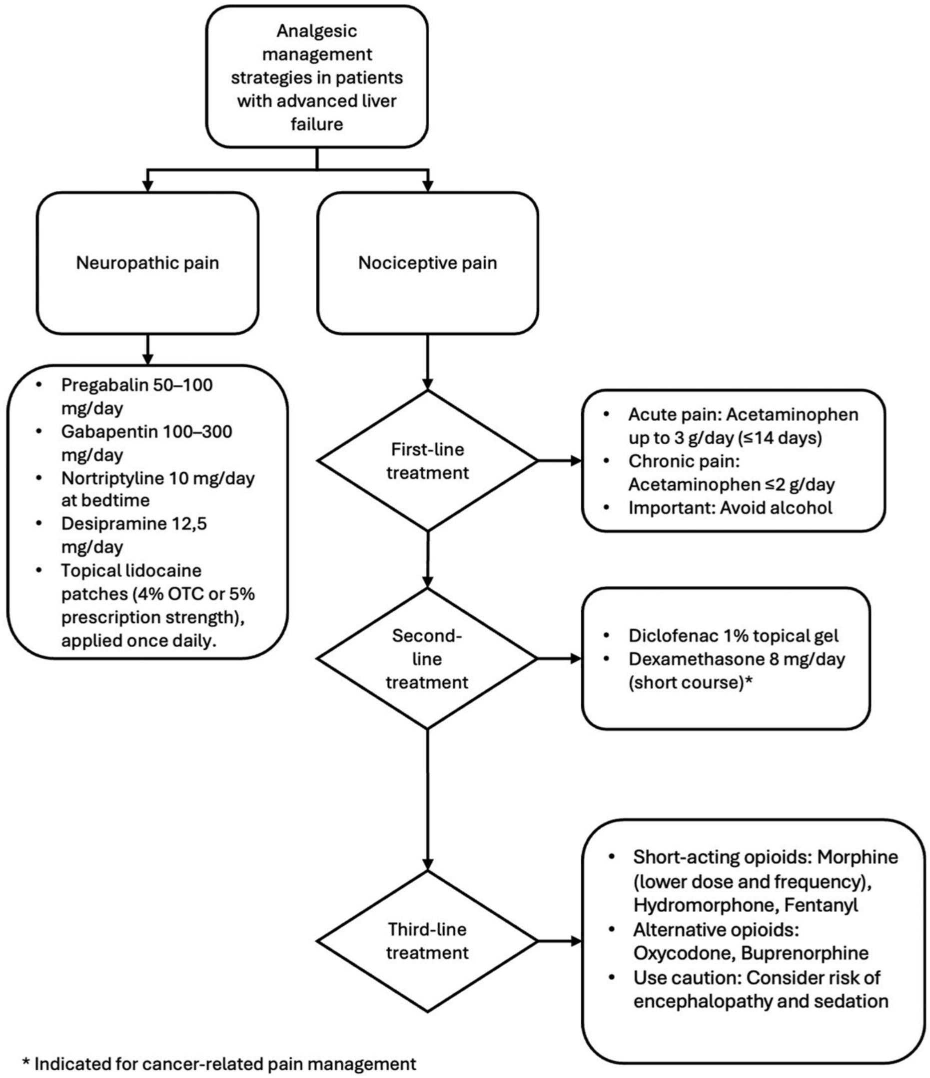

Figure 2. Flowchart of analgesic management strategies in patients with advanced liver failure.

Ascites

Ascites is the most common complication in decompensated cirrhosis, indicating advanced hepatic dysfunction (58). Ascites can be classified according to its severity: Grade 1 (mild ascites) if it is only detected by ultrasound; Grade 2 (moderate ascites) with moderate and symmetrical abdominal distension; and Grade 3 (extensive ascites) with marked abdominal distension and discomfort (59). The development of ascites is primarily driven by portal hypertension and a reduced effective circulating blood volume, which activate the renin–angiotensin–aldosterone system (RAAS). This activation triggers renin release from the kidneys, initiating a cascade that results in the production of angiotensin II and aldosterone. These hormones promote sodium and water reabsorption in the kidneys, leading to fluid accumulation in the abdominal cavity and the formation of ascites (60). Management follows a stepwise approach, including sodium restriction, diuretic therapy, large-volume paracentesis, and, in advanced cases, transjugular intrahepatic portosystemic shunt (TIPS) placement or liver transplantation (28,61).

Sodium restriction and diuretics. Initial management should begin with dietary sodium restriction to less than 2 grams per day. This helps achieve a negative sodium balance, which mobilizes ascitic fluid without causing malnutrition or metabolic disturbances. Fluid restriction is not recommended unless serum sodium falls below 125 mmol/L (61).

Diuretics are the cornerstone of pharmacologic therapy. Spironolactone, an aldosterone antagonist, is the first-line agent because it targets the hyperaldosteronism typical in cirrhosis (62). Start at 100 mg/day and titrate up to 400 mg/day if needed (63).

If spironolactone alone is insufficient or causes hyperkalemia, add a loop diuretic like furosemide, starting at 40 mg/day and increasing to a maximum of 160 mg/day (63). Diuretic doses should be reduced or withheld if renal insufficiency, severe hyponatremia (<120 mmol/L), encephalopathy, or muscle cramps occur (61).

Large-volume paracentesis and albumin. Large-volume paracentesis is the treatment of choice for tense (grade 3) ascites secondary to portal hypertension. It allows for rapid fluid removal and relieves symptoms such as abdominal distension, dyspnea, and pain. However, when ascites is related to hepatocellular carcinoma or another malignant process, management should be individualized, and the serum–ascites albumin gradient (SAAG) is recommended to help distinguish portal hypertension from malignant ascites (64).

To prevent post-paracentesis circulatory dysfunction, especially when >5 liters are removed, administer intravenous albumin at 6–8 g per liter of fluid drained. Albumin reduces the risk of renal failure and stabilizes hemodynamics by inhibiting activation of the RAAS (51).

Refractory ascites

Refractory ascites is defined as fluid that fails to respond to maximal diuretic therapy or recurs rapidly after paracentesis (62). Table 4 summarizes current treatment options.

Table 4. Treatment options for refractory ascite.

Treatment	Description
TIPS	Redirects portal blood flow to the systemic circulation, lowering portal pressure and facilitating ascites resolution. Its use is limited by the risk of hepatic encephalopathy, which may be induced or worsened (64).
Tunneled Peritoneal Catheter	Recommended for patients who cannot tolerate repeated paracentesis and are not candidates for TIPS, especially those with a prognosis of <3–6 months. It has low mortality and similar infection rates compared to large-volume paracentesis (65,66).
Implanted system for continual ascitic fluid removal	Continuously drains ascitic fluid into the bladder, allowing urinary elimination. Improves quality of life in refractory ascites, although it does not significantly prolong survival (64).
SGLT2 Inhibitors	Originally developed for type 2 diabetes, these agents promote natriuresis and enhance renal function, which may help reduce ascitic fluid accumulation in cirrhotic patients (64).

Abbreviations: TIPS: Transjugular Intrahepatic Portosystemic Shunt; SGLT2: Sodium-Glucose Cotransporter 2.

Hepatic encephalopathy

In patients with ESLD, management should aim to balance symptom relief with treatment burden, minimizing unnecessary hospitalizations and optimizing quality of life. The approach centers on three pillars: identifying and treating precipitating factors, reducing ammonia levels, and modulating cerebral inflammation (67).

Identification and treatment of precipitating factors. The first step in managing hepatic encephalopathy (HE) is to identify and correct triggering factors. These include infections, gastrointestinal bleeding, electrolyte imbalances, dehydration, excessive sedation, and constipation (58,67). Notably, several drug classes act as common precipitants. Central nervous system depressants, such as benzodiazepines and other psychoactive agents, exacerbate neuronal dysfunction through enhanced GABAergic activity. Similarly, opioids, anticholinergics, and barbiturates contribute via sedative effects and constipation, which facilitate ammonia accumulation. Excessive diuretic use may further precipitate HE by inducing dehydration and electrolyte imbalances (68). Addressing these factors is essential to resolve episodes and prevent recurrence.

Reduction of ammonia load. Hyperammonemia is the main driver of HE. Management relies on two primary strategies:

- **Non-absorbable disaccharides (lactulose, lactitol)** are first-line agents that reduce ammonia absorption by promoting fecal excretion. For acute hepatic encephalopathy, lactulose can be administered as a 30 g bolus and repeated hourly until the first bowel movement. For prevention of recurrence, it is typically given in syrup form at a dose of 10 to 20 g two to four times per day, titrated to achieve two to three soft stools daily (69). However, recent evidence suggests that polyethylene glycol (PEG) may offer superior efficacy for rapid resolution of acute encephalopathy episodes (18).

- **Rifaximin:** A non-absorbable antibiotic used as adjunct therapy for recurrent HE. It modulates gut microbiota and reduces systemic inflammation (550 mg every 12 hours) (70).

Other therapeutic options may be used selectively:

- **L-ornithine L-aspartate (LOLA):** Enhances ammonia detoxification via the urea cycle and skeletal muscle glutamine synthesis. It reduces HE severity but is not first-line.
- **Branched-chain amino acids (BCAAs):** Support protein synthesis and ammonia clearance in patients with chronic HE and sarcopenia (71).
- **Neomycin and metronidazole:** Alternatives to rifaximin, though their use is limited by toxicity and adverse effects with prolonged treatment (72).

Cachexia

Cachexia is a multifactorial clinical syndrome characterized by a continuous loss of skeletal muscle mass and adipose tissue that results in progressive functional decline (19). It is not solely the consequence of caloric deficiency but is also driven by systemic inflammation and altered metabolism mediated by disease-related factors. International consensus defines cachexia along a continuum (precachexia, cachexia, refractory cachexia), and its diagnosis is based on weight loss criteria—namely, >5% of body weight over 6 months, or >2% in patients with a body mass index (BMI) <20 kg/m^2. Cachexia is highly prevalent in advanced cirrhosis and ESLD, affecting up to 50% of patients (31). It is linked to poor outcomes, including higher infection risk, faster hepatic decompensation, and increased mortality (19).

Energy and protein requirements. Patients should receive 30–35 kcal/kg/day to prevent catabolism (73). Protein intake must be maintained at 1.2–1.5 g/kg/day. Protein restriction should be avoided, as it worsens sarcopenia and functional decline (73).

Nutritional management. Diets should include high-biological-value proteins (e.g., eggs, fish, poultry), and BCAA supplementation may help prevent HE and support muscle mass (73). Supplementation with fat-soluble vitamins (A, D, E, K) and trace elements (zinc, selenium, magnesium) is essential, especially in patients with cholestasis (73,74). Meals should be divided into 5–6 portions daily to prevent long overnight fasting, which accelerates muscle catabolism (73). A late-evening snack rich in complex carbohydrates (e.g., starches) helps maintain energy balance (73).

Pruritus

Pruritus affects up to 70% of patients with cholestatic liver disease, significantly impacting sleep and mental health (28,75). Management requires a stepwise strategy that includes both pharmacological and non-pharmacological interventions. Non-pharmacological strategies include the use of moisturizers and emollients, wearing loose-fitting cotton clothing, and applying cold compresses. Patients should also avoid heat exposure and histamine-rich foods such as chocolate and shellfish (76). UVA/UVB phototherapy may benefit selected patients, specifically those cases that are resistant to conventional therapies (76).

First-line pharmacologic treatments for cholestatic pruritus are bile acid sequestrants, such as cholestyramine (4–16 g/day) and colesevelam (3.75 g/day), which reduce bile acid reabsorption. If symptoms persist, rifampin (150–600 mg/day) can be added. These agents are effective when pruritus is associated with cholestasis (75). Liver function must be monitored, as the risk of hepatotoxicity is heightened in individuals with underlying liver disease (76,77). Naltrexone, a mu-opioid receptor antagonist, has shown efficacy in reducing pruritus by over 50% in some patients and may be initiated at 12.5 mg, titrated up to 150 mg daily, with close monitoring of liver function (75). However, opioid withdrawal is a common adverse effect; therefore, this treatment should be avoided in palliative care patients who are also receiving opioids. Gabapentin, despite less consistent results in hepatic pruritus, may be considered at starting doses of 100–300 mg/day, up to 2400 mg as tolerated (75).

In patients with associated depression, SSRIs like sertraline (75–100 mg/day) may provide symptomatic relief (75). Bezafibrate (200–400 mg/day) has also shown efficacy in cholestatic pruritus (75). For severe, refractory cases, albumin dialysis (MARS) may be considered (76). A comprehensive, individualized, and multidisciplinary approach is essential to optimize symptom control and improve patient well-being (76).

Dyspnea

Dyspnea is a common and distressing symptom in terminal-stage liver disease. It significantly impairs quality of life and often results from multiple contributing factors, including tense ascites, hepatic hydrothorax, anemia, sarcopenia, and metabolic disturbances linked to hepatic dysfunction (78). Fluid overload and elevated intra-abdominal pressure restrict diaphragmatic movement, worsening dyspnea and limiting physical activity (79).

Management should be comprehensive, combining pharmacologic and non-pharmacologic strategies. Sleep optimization, psychoeducational support, and pulmonary rehabilitation may improve exertional capacity and reduce perceived breathlessness. Adequate control of ascites and volume overload is critical to relieve diaphragmatic compression and improve ventilation (9).

Low-dose opioids, such as morphine or hydromorphone, can alleviate dyspnea by altering the perception of respiratory effort (3). In cases of anxiety-related dyspnea, benzodiazepines like lorazepam, oxazepam, and temazepam—metabolized via glucuronidation rather than hepatic oxidation—may be cautiously used, with close monitoring to avoid precipitating hepatic encephalopathy (80). Corticosteroids may be beneficial when inflammation or infiltrative processes contribute to symptoms (81).

For refractory dyspnea due to hydrothorax or massive ascites, paracentesis or thoracentesis can offer immediate relief (9). However, recurrence is common, requiring regular reassessment. TIPS may be considered in selected cases, but the decision should balance benefit against the risk of hepatic encephalopathy and hepatic reserve (81). Management must be individualized and interdisciplinary, with a focus on comfort and quality of life (79,82).

Psychological symptoms

Patients with ESLD frequently experience psychological symptoms, including anxiety, depression, insomnia, and cognitive dysfunction. These symptoms profoundly impact quality of life (83). Depression affects 30–40% of patients, emphasizing the need for early recognition and multidisciplinary care (13). Mental health screening should be performed early using validated tools to detect mood disturbances (20).

Pharmacologic treatment must consider hepatic function. SSRIs such as sertraline and escitalopram are preferred due to their favorable safety profile in cirrhosis, with fewer adverse effects than other antidepressants (13). For severe anxiety, benzodiazepines should be used with caution due to the risk of precipitating hepatic encephalopathy. Safer alternatives include low-dose quetiapine, hydroxyzine, or pregabalin, with appropriate dose adjustment (9). Melatonin may improve sleep quality without affecting hepatic metabolism (9). Other options include antihistamines like hydroxyzine and short-term use of zolpidem, though the latter requires caution due to potential risks of memory impairment and hepatic encephalopathy (84). Psychotherapeutic interventions, including cognitive-behavioral therapy and acceptance and commitment therapy, have shown efficacy in reducing psychological distress. Early palliative care involvement supports emotional adjustment and enhances overall quality of life (85). Patient and family education, along with participation in support groups, are key tools to address the psychological burden of terminal liver disease (13).

Hospice and end-of-life eligibility criteria

Eligibility for hospice in terminal ESLD is based on clinical deterioration and limited life expectancy. Prognostication remains difficult due to

Table 5. CMS hospice eligibility criteria for patients with liver disease.

Criterion	Description
1. The patient should show both a and b:	a. Prothrombin time prolonged more than 5 s over control, or International Normalized Ratio (INR) > 1.5 b. Serum albumin < 2.5 g/dl
2. End-stage liver disease is present, and the patient shows at least one of the following:	a. Ascites, refractory to treatment or patient noncompliance b. Spontaneous bacterial peritonitis c. Hepatorenal syndrome (elevated creatinine and blood urea nitrogen (BUN) with oliguria (<400 ml/day) urine and sodium concentration <10 mEq/l) d. Hepatic encephalopathy, refractory to treatment, or patient noncompliance e. Recurrent variceal bleeding, despite intensive therapy
3. Documentation of the following factors will support eligibility for hospice care:	a. Progressive malnutrition b. Muscle wasting with reduced strength and endurance c. Continued active alcoholism (>80 g ethanol/day) d. Hepatocellular carcinoma e. Hepatitis B virus surface antigen (HBsAg) positivity f. Hepatitis C refractory to interferon treatment

Source: Adapted from Centers for Medicare & Medicaid Services (CMS).

the unpredictable trajectory of hepatic failure, but established criteria can guide referral to palliative and hospice services (21). Centers for Medicare & Medicaid Services (CMS) hospice eligibility criteria can aid clinicians in identifying patients with ESLD who may benefit from referral to hospice and end-of-life care services. These criteria incorporate objective markers of hepatic function and clinical complications commonly seen in terminal ESLD (Table 5).

Beyond clinical indicators, patient and family perspectives must be prioritized. Shared decision-making—rooted in understanding disease status and care preferences—is essential for effective end-of-life planning (85). A comprehensive approach that includes emotional support, symptom control, and respect for patient autonomy is vital to ensure a dignified and compassionate transition to hospice care (86).

Discussion

ESLD poses a major clinical challenge due to its high symptom burden and poor prognosis. Despite strong evidence supporting early PC, its integration into ESLD care remains limited (14,40). Misconceptions that PC is only for terminal phases, uncertainty about disease progression, and lack of standardized referral criteria contribute to this gap (36). Compared to cancer, where PC is routinely integrated, ESLD patients often receive delayed or insufficient support (22), despite experiencing similar or greater symptom burdens (13). Qualitative studies describe patients feeling uninformed, fearful, and unsupported during advanced stages of disease (23,83).

Structural and cultural barriers hinder PC delivery in ESLD. These include limited training for hepatologists, fragmented care systems, and poor communication between specialties (15,36). Multidisciplinary collaboration is crucial. Interdisciplinary liver-palliative teams can ensure coordinated symptom management, psychosocial support, and decision-making aligned with patient values. Donlan et al. (23) emphasize that patients and caregivers prioritize emotional support, clear prognostic communication, and continuity of care—elements often lacking when PC is delayed.

Symptom management in ESLD is complex and requires individualized strategies. Pain, pruritus, and hepatic encephalopathy remain challenging due to altered pharmacokinetics and overlapping complications. Rakoski et al. (52) note persistent gaps in pain control practices. Similarly, nutritional interventions and dyspnea management are frequently underutilized, despite being central to quality of life (73,75,82).

Our findings underscore the need for hepatologists to adopt proactive identification of palliative needs using clinical indicators such as MELD ≥20, particularly when accompanied by severe complications such as refractory ascites, persistent hepatic encephalopathy, recurrent variceal bleeding, or type 1 hepatorenal syndrome (see Table 5) (16).

Additionally, CLIF-C scores and the presence of a high symptom burden, both commonly used for prognostication in ESLD, could guide timely referrals to palliative care, especially for patients ineligible for transplantation (5). Integrating these scores into electronic health record alerts or multidisciplinary tumor boards—specifically in cases of ESLD secondary to hepatocellular carcinoma or liver metastases—may help operationalize early PC pathways and standardize decision-making across services. Findings support policies that prioritize early PC integration, particularly for patients with significant frailty or frequent hospitalizations (6). Establishing dedicated liver–palliative care units may further bridge the gap between hepatology and supportive care (87).

Clinically, patient-centered approaches require recognizing that not all ESLD patients are transplant candidates. For these individuals, the goal should shift from curative intent to maximizing comfort, function, and autonomy. Beresford et al. (83) propose a "possible care" model, grounded in realistic goals and compassionate communication.

Furthermore, hepatology training programs should incorporate foundational principles of PC to improve provider confidence not only in managing complex symptoms and initiating prognostic conversations, but also in integrating a palliative approach throughout the disease trajectory. This integration supports the development of personalized treatment and care plans, shifting the focus from solely identifying poor prognosis to promoting early, patient-centered interventions. This could address the hesitancy and variability observed in practice (29). Prospective multicenter trials are needed to evaluate the impact of early PC across liver disease stages. More meta-analyses incorporating data from underrepresented regions, such as low- and middle-income countries, sub-Saharan Africa, and rural areas, would improve the generalizability of the findings, ensuring they are more applicable to diverse populations. Importantly, qualitative research on patient and caregiver perspectives—such as those by Donlan et al. (23) and Beresford et al. (83)—is essential for designing care models that truly reflect lived experiences and address emotional, existential, and practical needs.

Furthermore, we acknowledge that health system structures, clinical workflows, and access to palliative resources vary significantly across regions. Thus, while this review emphasizes early integration strategies and clinical indicators, their application should be adapted to local resources, care structures, and cultural expectations.

This review has limitations inherent to its narrative design. Additionally, the inclusion of studies published only from 2015 onward may have excluded relevant earlier literature. While a systematic and rigorous search strategy was used, the heterogeneity of study populations, intervention types, and outcome measures limited direct comparison across findings. Additionally, the reliance on published data may not fully capture variations in clinical practice or patient experiences in low-resource or non-specialist care settings.

Conclusions

End-stage liver disease is a complex condition marked by severe symptoms and poor prognosis. This review underscores the urgent need to integrate palliative care systematically and proactively into patient management—beyond viewing liver transplantation as the only therapeutic path. Timely palliative care improves symptom control, reduces preventable hospitalizations, strengthens shared decision-making, and enhances quality of life for both patients and families. Despite growing recognition of its benefits, structural, educational, and cultural barriers continue to limit implementation. Health systems must address these gaps by supporting interdisciplinary team development, establishing clear referral criteria, and promoting education for both healthcare providers and the public. A care model that prioritizes dignity, comfort, and patient autonomy must become a core component of modern liver disease management.

Ethical considerations

This literature review analyzed studies previously approved by relevant ethics committees. As it primarily involved secondary reviews, the responsible use of published information was ensured, with strict adherence to principles of confidentiality and scientific rigor in analyzing the originally reported data.

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ORCID

Daniela Sarria-Gómez http://orcid.org/0009-0006-7008-0423
Cristhian Camilo Martínez Torres http://orcid.org/0000-0001-6739-0232
Diana Estrada-Bermúdez http://orcid.org/0009-0008-1349-0324
Liliana Saavedra http://orcid.org/0009-0003-6034-0779

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