

Palliative Care in End-Stage Liver Disease Patients Awaiting Liver Transplantation: Review

Sara Vieira Silva^{a, b} Elga Freire^{a, b} Helena Pesseguero Miranda^{b–d}

^aEquipa Intra-Hospitalar de Suporte de Cuidados Paliativos, Serviço de Medicina, Centro Hospitalar e Universitário do Porto, Porto, Portugal; ^bInstituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Porto, Portugal; ^cUnidade de Transplantação Hepato-bilio-pancreática, Centro Hospitalar e Universitário do Porto, Porto, Portugal; ^dInstituto de Saúde Pública da Universidade do Porto (ISPUP), Universidade do Porto, Porto, Portugal

Keywords

Palliative care · End-stage liver disease · Liver transplantation

Abstract

Introduction: End-stage liver disease (ESLD) is the advanced phase of most liver diseases. The cure is liver transplantation (LT), only available for a minority of patients. This review summarizes the evidence regarding palliative care (PC) in ESLD patients awaiting LT. **Methods:** Review of the literature available in Medline, Scopus and Web of Knowledge, with keywords ESLD and PC. **Results:** Fifteen of the 230 articles reviewed met the inclusion criteria. Ten main themes were addressed: symptom burden; perspectives of life-sustaining treatment and comfort for patients, families and health professionals; goals of care discussions; patient and family needs; quality of life; PC and survival; referral to PC, barriers and opportunities; integration of PC; outpatient care and cost-effectiveness analysis. The referral of patients to PC was only evaluated in a few studies, all of which reported low referral rates. Better knowledge of how PC professionals can support other professionals was considered important, and also better ways to integrate PC were considered essential.

Conclusion: ESLD patients awaiting LT have a significant need for PC and, despite the insufficient response, were reported to benefit from this type of care. Future research is essential to determine the means to overcome barriers and better integrate PC for ESLD patients awaiting LT.

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Cuidados Paliativos nos doentes com Doença Hepática avançada que aguardam transplante hepático: revisão

Palavras-Chave

Cuidados paliativos · Doença hepática avançada · Transplante hepático

Resumo

Introdução: A doença hepática avançada (DHA) corresponde à fase mais avançada das doenças hepáticas. O transplante hepático (TH) é o tratamento curativo, disponível apenas para uma minoria de doentes. Esta revisão

sumariza a evidência sobre cuidados paliativos (CP) em doentes com DHA que aguardam TH. **Métodos:** Revisão da literatura existente na Medline, Scopus e Web of Knowledge. Palavras chave pesquisadas CP e DHA. **Resultados:** Quinze dos 230 artigos encontrados cumpriram critérios de inclusão. Dez temáticas foram abordadas: carga sintomática; discussão de objetivos de cuidados; perspectivas sobre tratamentos de suporte artificial e conforto; necessidades do doente e família; qualidade de vida; CP e impacto no prognóstico; referência para CP, barreiras e oportunidades; integração dos CP; cuidados de ambulatório e análises de custo-benefício. Poucos estudos avaliaram a referência para CP, todos com baixas taxas. Mais conhecimento e formação dos profissionais que acompanham doentes com DHA parece ser necessário, bem como, melhor articulação entre os diferentes intervenientes. **Conclusão:** Doentes com DHA que aguardam TH apresentam importantes necessidades de CP. Apesar da insuficiente resposta a este nível, parecem beneficiar deste tipo de cuidados. Estudos futuros que clarifiquem como ultrapassar as barreiras e a melhor integração dos CP nos doentes que aguardam TH são essenciais.

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Introduction

End-stage liver disease (ESLD) is the advanced phase of most liver diseases and is characterized by the complications of liver disease [1]. It is responsible for almost 2% of all deaths and is currently the 7th leading cause of death at the European level [2]. ESLD is the leading cause of organ failure amongst the population under 65 years [3], thus corresponding to a very significant loss of years of potential life. Episodes of decompensation have a significant impact on mortality, and it is estimated that, after the first episode, mortality at 5 years may reach 85% [4]. The only effective treatment is liver transplantation (LT), available for a minority of patients.

Previous studies have shown that ESLD patients usually present with high symptom prevalence [5], similar to patients with other advanced diseases such as cancer, heart or respiratory failure. Symptom burden associated with LT complexity and the high risk of mortality suggest significant palliative care (PC) needs for ESLD patients. Despite these important needs, PC referral remains low and the available data are scarce [6]. In one of the rare known studies [7], only 10% of the patients excluded from the transplant list were referred for PC. Little is

known about the remainder of ESLD patients and specifically about PC for patients awaiting LT.

This review summarizes the available evidence-based literature regarding PC in ESLD patients awaiting LT.

Methods

We conducted a review in order to scan the current literature and identify the nature and extent of research evidence related to PC in ESLD patients awaiting LT. The review was carried out by one reviewer and was supervised by two experts, one hepatologist and one PC specialist.

Search Strategy

We searched for evidence-based articles in the following electronic databases: Medline (PubMed), Scopus and Web of Knowledge. The search strategy was limited to all English language articles published until June 6, 2019. The terms “palliative care” and “end-stage liver disease” were used as keywords. The key concepts resulted in 25 articles in Pubmed, 84 articles in Scopus and 115 articles in Web of Knowledge. Additionally, 6 studies were found after searching the references or articles included from the search databases.

Inclusion Criteria

Only studies involving PC in ESLD patients and a population over 18 years old were included.

Exclusion Criteria

Articles written in languages other than English were excluded. Editorials, letters to the editor, comments and narrative case reports were excluded, as well as articles that did not include patients waiting for LT.

Data Synthesis and Data Collection Process

Detailed information of the articles included was categorized by major themes: symptom burden; perspectives of life-sustaining treatment and comfort for patients, families and health care professionals; goals of care discussions; patient and family needs; quality of life; PC and survival; referral to PC, barriers and opportunities; integration of PC; outpatient care and cost-effectiveness analysis. Data extraction was done manually, without resorting to any extraction software. Quality review was not assessed as the purpose of this review is to scan the current literature in order to determine what has been reported and what needs to be investigated related to PC in ESLD patients awaiting LT.

Results

A total of 230 articles were reviewed for inclusion using the keywords. The articles were then screened and further eliminated after reviewing the abstracts, with 89 retained for further reading. Of these, only the 15 articles that met the inclusion criteria were selected. A flow dia-

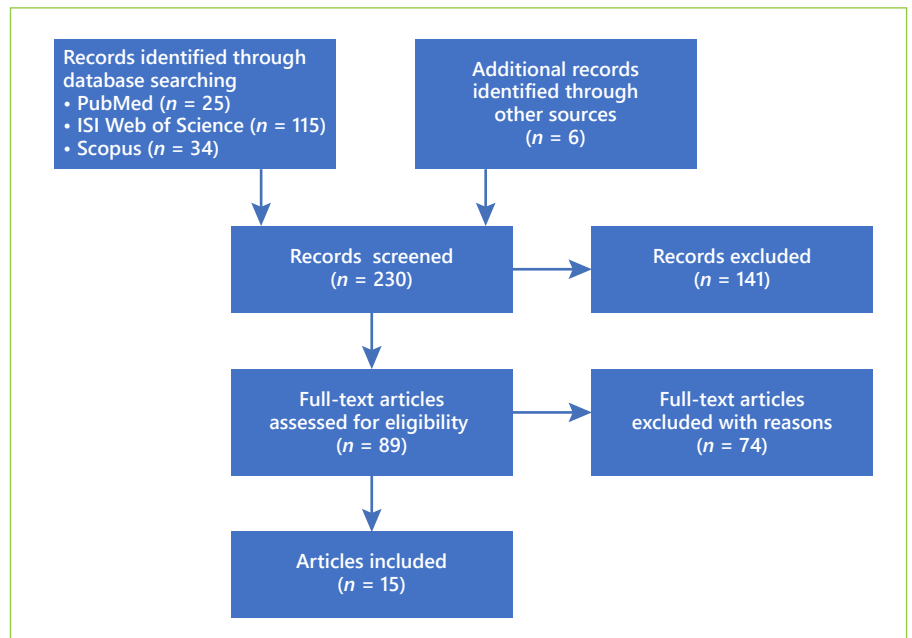


Fig. 1. PRISMA flow diagram showing the literature method search. *n*, number of articles.

gram following PRISMA guidelines [8] showing all literature procedures as well as the resulting number of articles selected is displayed in Figure 1. An overview of the 15 articles included is presented in Tables 1 and 2 with the articles organized according to publication date [9–23]. Data gathered from the articles were summarized using percentages and frequencies for descriptive purposes.

Most studies originated in North America ($n = 12$) or in Europe ($n = 3$). Studies predominantly used quantitative ($n = 9$) or mixed ($n = 4$) designs. We found only surveys, mostly prospective ($n = 11$).

Study populations included patients, carers and health care professionals. The male gender predominated, and the median age of patients ranged from 51 to 62 years. Ten main themes were addressed: symptom burden; perspectives of life-sustaining treatment and comfort for patients, families and health care professionals; goals of care discussions; patient and family needs; quality of life; PC and survival; referral to PC, barriers and opportunities; integration of PC; outpatient care and cost-effectiveness analysis.

Symptom Burden

Few studies addressed directly symptoms in ESLD patients awaiting LT. An early PC intervention study has found that the most commonly reported symptoms were fatigue, sleep disorders and pruritus [9]. In another study patients reported lack of energy, pain, sleep disorders and

drowsiness as the most frequent, severe and distressing symptoms [10]. Other frequent and severe symptoms were dry mouth, lack of concentration and itching. Lack of concentration was considered more distressing than dry mouth.

A qualitative interview study of patients and bereaved carers found deteriorating physical health was compounded by ongoing psychological issues, commonly relating to alcohol dependence, including depression and guilt related to the nature of the disease [11].

Attitudes toward symptom management, such as pain in ESLD patients, were evaluated and showed that 30–40% of participants, despite having moderate pain, reported using no pain medication. The patient who used it reported having less than 50% relief and were only moderately satisfied with their overall pain treatment. Moreover, although 8 out of the 11 patients who were not LT candidates took a strong opioid, only 2 out of the 9 patients awaiting LT were given the same pain relief treatment [12]. In a survey of LT service providers [13], nurses, postgraduate year 1 medical and surgical trainees were less likely to agree that LT providers were proficient in managing pain and depression than attending physicians. Also, postgraduate year 1 medical and surgical trainees (86%) and attending physicians (100%) were reported more likely to avoid using opioid medication to treat pain in these patients than nurses (62%) ($p = 0.0001$).

Table 1. Data extracted from included studies

Author's name	Publication date	Design	Country	Population	Diagnosis of liver disease	Setting	Patients, n	Subthemes	Main findings
Medici et al. [20]	2008	Prospective	USA	ESLD patients	Virus (HCV, HBV) 25, alcohol 27, virus and alcohol 42, ESLD and HCC 44, other 12, unknown 9	Hospice	157 ESLD patients (15 listed for LT)	Referral to PC, barriers and opportunities; PC, LT and survival	Significant correlation between the MELD score and length of stay in the hospice service; possibility of a new integrated model between the hospice, PC team and LT team
Walling et al. [15]	2013	Retrospective	USA	ESLD patients	Not specified	Academic medical center	79 ESLD (13 considered for LT)	Symptom burden; goals of care discussions; perspectives of life-sustaining treatment and comfort for patients	Data suggested that patients who died awaiting transplantation have greater unmet needs of PC and receive relatively aggressive care during their terminal hospitalization
Hansen et al. [12]	2014	Prospective	USA	ESLD patients	Virus (HCV, HBV) 10, alcohol 5, HCV and alcohol 2, NASH 1, unknown 2	Outpatients at an academic medical center	20 ESLD patients	Symptom burden (pain); outpatient care	Interindividual and intraindividual variability of Brief Pain Inventory over time; detailed assessment of individual patient pain characteristics, intake of pain medication, and use of complementary and alternative therapies should be completed by health professionals at each clinic appointment
Hansen et al. [10]	2015	Prospective	USA	ESLD patients	Virus (HCV, HBV) 10, alcohol 5, HCV and alcohol 2, NASH 1, unknown 2	Outpatients at an academic medical center	20 ESLD patients	Symptom burden; outpatient care	ESLD patients experience variability in physical and psychological distress over time; pain, lack of energy, feeling drowsy and difficulty sleeping were the most common symptoms
Walling et al. [23]	2015	Prospective	USA	ESLD patients	Not specified	Hospital (Veterans Affairs Health System)	110 ESLD patients (57 considered for LT)	Referral to PC, barriers and opportunities; integration of PC	Active case finding improved consideration for LT without decreasing PC consultation
Baumann et al. [9]	2015	Prospective	USA	ESLD patients	Virus (HCV) 33, alcohol 23, NASH 10, other 10, unknown 5	Outpatients at an academic medical center	50 ESLD patients considered for LT	Symptom burden; integration of PC; outpatient care	Early PC intervention counteracts the progressive worsening of ailing symptoms and specifically improved pruritus, well-being, appetite, anxiety and fatigue; PC intervention also decreased depression
Kathpalia et al. [17]	2016	Retrospective	USA	ESLD patients	Virus (HCV) 43, alcohol 11, HCV and alcohol 21, others 32	Liver transplant center	107 ESLD patients listed for LT	Referral to PC, barriers and opportunities	PC services are grossly underutilized in older, nonwhite patients with cirrhosis on liver transplant waiting list
Rush et al. [18]	2017	Retrospective	USA	ESLD patients	Not specified	Hospitals (nationwide inpatient sample)	39,349 ESLD patients	Referral to PC, barriers and opportunities	Use of PC consultation increased from 0.97% in 2006 to 7.1% in 2012; lower rates of referral associated with Hispanic ethnicity and health insurance coverage; higher socioeconomic status, DNR status, concurrent cancer diagnoses and treatment in large teaching hospitals were associated with increased rates of referral

Table 1 (continued)

Author's name	Publication date	Design	Country	Population	Diagnosis of liver disease	Setting	Patients, n	Subthemes	Main findings
Patel et al. [19]	2017	Retrospective	USA	ESLD patients	Not specified	Hospitals (national inpatient sample)	59,687 ESLD patients	Referral to PC, barriers and opportunities; cost-effectiveness analysis	PC consultation utilization was low but increased, total costs of hospitalization for ESLD also increased; PC consultation was associated with lower costs and procedure burden at the end of life; transplantation listing or receipt was associated with lower odds of receiving inpatient palliative care
Hudson et al. [11]	2018	Prospective	UK	ESLD patients, carers	Alcohol 8, NASH 4	Day-case paracetamol service at an academic center	17, 12 ESLD patients, 5 carers	Referral to PC, barriers and opportunities, patient and family needs; outpatient care	The needs of patients with ESLD and their carers towards the end of life include disabling physical symptoms, psychological distress, addiction, financial hardship and social isolation Health care services available to patients with ESLD are centered in secondary care, focus on disease-modifying approaches and provide support once curative options are exhausted; the end-of-life needs of patients with ESLD and their carers are frequently incompatible with the health care systems available to address them

ESLD, end-stage liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LT, liver transplantation; PC, palliative care; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; DNR, do not resuscitate.

Perspectives of Life-Sustaining Treatment and Comfort for Patients, Families and Health Care Professionals

An intensive care unit prospective study that included 6 patients (all considered for LT), 19 family members and 122 health care professionals revealed that the decision trajectory and the reasoning behind the life-sustaining treatment and comfort care decisions are resumed by the metaphor “on the train” [14]. The use of this expression enabled patients and family members to conceptualize their experience of the decision-making process – patients and families are in the train, where each life-sustaining treatment decision is a “train station,” a place where they can theoretically choose to disembark but they feel that they have little choice to do it. In the same study, Hansen et al. [14] stated that 4 subthemes became evident during the patients’ stay in the intensive care unit: (i) for families, life was the obvious answer, the purpose of life-sustaining treatment decisions was to keep the patient alive and headed toward the goal of LT; (ii) excluding families from “minor” life-sustaining treatment decisions added to their limited preparedness for major ones that followed; (iii) multiple professionals, each with a narrow focus, infrequently explained to family members how the function of an organ interrelated with the function of other organs or what it meant in the context of the overall picture of the patient’s illness; (iv) different perceptions of the patients’ illness course among specialities, between professions, and between professions and patients/families.

A structured PC intervention study in the surgical intensive care unit showed that, during the intervention period, the number of patients without resuscitation status significantly increase over time amongst those who died (from 52 to 81%, $p = 0.03$) [15]. The mean length of stay decreased, both in those who died and those who survived in the intensive care unit. Withdrawal of ventilator, pressors and nutritional support increased significantly in the intervention period.

Goals of Care Discussions

Goals of care discussions seem to be less common in patients considered for LT [15], and we found different perspectives from different professionals in the survey of Beck et al. [13]: a vast majority of nurses (96%) and post-graduate year 1 medical and surgical trainees (91%) responded that it was appropriate to hold goals of care discussions during clinical visits with the patient’s primary care provider, while only about a third of attending physicians (31%) agreed ($p = 0.0001$). In contrast, more attend-

Table 2. Data extracted from included studies (with health care professionals)

Author's name	Publication date	Design	Country	Population	Diagnosis of liver disease	Setting	Participants, n	Subthemes	Main findings
Hansen et al. [14]	2012	Prospective	USA	ESLD patients, carers, health care professionals	Virus (HCV) 3, autoimmune hepatitis 1, primary sclerosing cholangitis 1, unknown 1	Hospitals (university medical center and Veterans Affairs Medical center)	6 ESLD patients being evaluated or on the list for LT, 19 family members, 122 health care professionals	Perspectives of life-sustaining treatment and comfort for patients, families and health professionals	Health care professionals generally do not share with family members the minor life-sustaining treatment decisions or how they played into the overall picture of the patient's illness Patients' and family members' understanding of life-sustaining treatment decisions is lacking "Mismatches" among specialties, between professions, and between professions and patients/families in perspectives on events related to patients at the end of life have been documented
Lamba et al. [16]	2012	Prospective	USA	ESLD patients, carers, health care professionals	Not specified	Intensive care unit of an academic, tertiary care, public hospital-based liver transplant center	104 patients (35 ESLD, 48 recent LT, 21 remote LT)	Symptom burden; goals of care discussions; perspectives of life-sustaining treatment and comfort for patients, families and health professionals; integration of PC; quality of life	Goals of care discussions on physician rounds increased from 2 to 38% of patient-days During the intervention, although mortality rates were unchanged, DNR status increased; withdrawal of life support increased; DNR was instituted earlier; admission to DNR decreased; DNR to death time increased; intensive care unit mean length of stay decreased Family responses suggested more "time with family"/"time to say goodbye"
Low et al. [22]	2015	Prospective	UK	Health care professionals	-	Liver professional, specialist PC and general practice	195 liver professional, 273 specialist PC, 46 general practice professionals	Referral to PC, barriers and opportunities; integration of PC; outpatient care	All professions acknowledged the role of specialist PC in caring for those dying with cirrhosis and need for further training to improve confidence and enable joint working between specialist PC, general practice and liver teams; symptom management, prognostication and overall service structure were identified as key areas for future research
Beck et al. [13]	2016	Prospective	USA	Health care professionals	-	Academic medical center	88 LT providers (47 intensive care nurses, 22 postgraduate year 1 medical and surgical trainees and nurse trainees, 19 attending physicians)	Goals of care discussions; perspectives of life-sustaining treatment and comfort; referral to PC, barriers and opportunities; quality of life	LT providers overwhelmingly report that PC benefits patients and is consistent with LT goals, even while patients are listed for LT; barriers to PC include confusion over referral criteria and describing PC as end-of-life care by attending physicians

Table 2 (continued)

Author's name	Publication date	Design	Country	Population	Diagnosis of liver disease	Setting	Participants, n	Subthemes	Main findings
Standing et al. [21]	2017	Prospective	UK	Health care professionals	-	Primary care	25 GPs	Goals of care discussions; perspectives of life-sustaining treatment and comfort; referral to PC, barriers and opportunities; outpatient care	Many GPs expressed a desire to be more closely involved in end-of-life care; main constraints identified: those relating directly to the condition (symptoms), issues arising from patients' social circumstances and deficiencies in the organization and delivery of services; GPs agreed that at the end of life patients with liver disease ideally need primary care and hospital specialists to work closely together

ESLD, end-stage liver disease; HCV, hepatitis C virus; LT, liver transplantation; PC, palliative care; DNR, do not resuscitate; GPs, general practitioners.

ing physicians (69%) thought it was appropriate for a patient's hepatologist to have goals of care discussions during clinical visits, with 100% of nurses and 91% of postgraduate year 1 medical and surgical trainees agreeing.

PC intervention studies revealed different results: in the intensive care unit [15] setting goals of care discussion increased from 2 to 39%, while in an outpatient early PC intervention study [9] it did not significantly increase rates of advance directive documentation.

Patient and Family Needs

Patients with ESLD who die while awaiting transplantation seems to have greater unmet needs for PC than other decedents, even if all received relatively aggressive care during their terminal hospitalization [15].

Two studies addressed indirectly some patient and family needs [11, 21]. Physical health problems and ongoing psychological issues (related or not with alcohol and other dependences) were identified as associated to physical disability, financial insecurity and the risk of increasing isolation [11]. Some patients feared advance care planning would result in a loss of hope and referred uncertainties about disease trajectory. Regarding LT, being assessed unsuitable was considered as an uniquely difficult period [11]. Families were perceived to be in need of support themselves, requiring frequent reassurance as the patient's condition deteriorated [21]. Caregiving was associated with psychological distress (particularly relating to ongoing alcohol use and hepatic encephalopathy) and deprioritization of individual needs [11].

Quality of Life

None of the selected articles assessed quality of life directly. Beck et al. [13] reported that patients and their families value goals of care discussions and were grateful for PC. Responses from the Family Quality of Dying and Death questionnaire, after a structured PC intervention in the surgical intensive care unit [15], revealed a trend toward improvements in "time with family and friends," breathing comfort, spiritual services, presence at time of death and overall physician care.

PC, LT and Survival

The study of Medici et al. [20] reported that 4 of the 6 transplanted patients experienced an improvement of their MELD score during hospice stay, suggesting that this service can potentially provide effective care to terminally ill patients. None of the other studies revealed data regarding the impact of PC on prognosis.

Referral to PC, Barriers and Opportunities

The included studies revealed different rates of referral of ESLD patients to PC, ranging from 4.5 to 29.1% [13, 17, 18], with an increasing tendency over the past 10–15 years [13, 18, 19].

Specifically from patients awaiting LT who died, only 2% received PC consultation [13] and in a nation-wide US weighted sample of 59,687 patients dying in the hospital with decompensated liver disease from 2009 to 2013, 18,027 (29.1%) received a PC consultation during the hospitalization and 331 patients were awaiting or received LT (1.9%) [19]. A study about the utility of the MELD (Model for End-Stage Liver Disease) score in transplant candidates and simultaneous hospice referral described a 5% rate (8/157) of referral to hospice care [20].

Factors associated with low PC referral included African-American, Hispanic and Asian ethnicity [18, 19] and absence of insurance coverage [18]. Factors associated with increased referral to PC were older age [17, 18], Caucasian ethnicity [17], “do not resuscitate” status [18], treatment in a teaching hospital [18, 19], in medium [18] and large-sized hospitals [18, 19], presence of hepatocellular carcinoma [18], presence of metastatic cancer [18], higher MELD score at listing [17, 20] and at delisting [17] and higher Charlson comorbidity index [19]. Decedents who were listed or received LT during admission were also less likely to receive PC than those who were not listed for LT [19].

Late referrals to PC among patients who died awaiting transplantation were identified by Kathpalia et al. [17], who found that the median number of days between PC consultation and death was 4. Different perspectives were identified by Beck et al. [13] among different professional groups, with nurses (88%) and postgraduate year 1 medical and surgical trainees (63%) being more likely than attending physicians (44%) to report that there were patients for whom they wished they had consulted PC earlier ($p = 0.001$). Attending physicians were less likely than nurses or postgraduate year 1 medical and surgical trainees to agree that it is appropriate to consult PC when the patient is diagnosed with ESLD, when the patient is listed for transplantation or when a patient with ESLD is admitted to the hospital for any reason. In contrast, the majority of attending physicians agreed that it is appropriate to consult PC when the patient is imminently dying [13]. In another study, the majority of LT service surgeons felt that PC should have been introduced earlier in the patient course, but only a few considered that there was a delay in the institution of PC under their care [15].

Attending physicians, more than any other group, were identified by all respondents (including attending physicians themselves), as creating a barrier to involving PC in the care of their patients [13]. In addition, they were much more likely than nurses and postgraduate year 1 medical and surgical trainees to identify the patient and family members as creating a barrier to PC consultation. Many respondents cited lack of clear criteria for involving PC and difficulty prognosticating end of life in ESLD patients as significant barriers. In a qualitative study involving general practitioners from the UK [21], the main concerns identified were those relating directly to the condition (symptom management and the need to combine a PC approach with ongoing medical interventions), issues arising from patients' social circumstances (stigma, social isolation and the social consequences of liver disease) and deficiencies in the organization and delivery of services.

Benefits of PC were verified on life-sustaining treatments [19], goals of care discussions [15] and symptom management reported in the early PC intervention study [9]. As a matter of fact, these studies found a 50% improvement of the initial moderate-to-severe pruritus, and of the general well-being, appetite, anxiety and fatigue. Pain, myalgia, sexual dysfunction, sleep disturbance and dyspnea also showed improvement, but this improvement did not reach statistical significance, and the early intervention also decreased depression (27.8%). An American study identified a significantly lower mean of total costs and length of stay for patients who received PC consultation in its terminal hospitalization, with an association of PC consultation with reduced hospital length of stay and reduction in nearly all procedures [19].

Integration of PC

A qualitative study on the incompatibility of health care services and end-of-life needs in advanced liver disease reported that patients relied on hospital services for most aspects of care, with general practitioners often being bypassed in decision-making and perceived as being unaware of ongoing developments [11]. On the other hand, general practitioners consider themselves as likely to have an established relationship with the patient and a greater understanding of their social situation and needs, whereas specialists offer expert knowledge on liver disease and treatment options [21]. They highlighted the importance that primary care physicians place on being able to provide a coordinating role but only when supported by members of the specialist teams. Managing complex and unusual symptoms, or judging when to introduce a PC approach, for instance, would benefit

from this collaboration. Collaborative working with the support from specialist hospital clinicians was regarded as essential, with general practitioners acknowledging their own lack of experience and expertise in this area. Further training of general practitioners and PC professionals on issues specific to liver disease were referred in another study [22]. Improved awareness of supportive care on symptom control, advanced communication and prognosis discussion for all professionals, and better knowledge of how PC professionals can support general practitioners and liver specialists were also referred as important measures [22]. A study of proactive case finding to improve concurrently curative and PC in patients with ESLD showed that patients in the quality improvement project were more likely to be considered for LT (77.6%, $p < 0,001$), to have their transplant evaluation completed (22.4%, $p = 0,01$) and to receive PC (62.5%, $p = 0.38$) [23].

Outpatient Care

Of the 15 studies selected, 1 took place in the hospice [20], 8 studies exclusively included inpatients [13–19, 23] and 4 studies were developed in the outpatient setting [9–12]. Of the 4 studies that included only health care professionals, 2 also considered the outpatient context [21, 22].

From the published results it is not possible to assess that there are differences between the needs of inpatients and those of outpatients. Baumann et al. [9] reported that after the early palliative care intervention in the outpatient setting, 50% of moderate to severe symptoms improved and 43% of patients showed improvement in clinically significant depressive symptoms, greater in those with more symptoms.

In another 2 studies [21, 22], many general practitioners felt unable to manage advanced cirrhosis in the community. All health care professional groups seem to wish to increase community provision of PC support and recognized that they required further training to improve their skills in caring for people with ESLD [22]. Service configuration was one of the key areas identified for future research [22].

Cost-Effectiveness Analysis

Based on the National Inpatient Sample (national data set across the USA) having been listed or receiving LT during the hospitalization was associated with higher overall costs compared to the unlisted status [19]. In this study, Patel et al. [19] reported that PC consultation was associated with lower costs and procedure burden at the end of life.

Discussion

We have identified 15 studies which met the inclusion criteria. Studies were quite diverse on themes, including symptom burden in ESLD patients to life-sustaining treatment decisions or integration of PC. There were also differences on the populations studied, all studies included patients with ESLD awaiting LT, but some also included noneligible LT patients. The authors found no randomized controlled trials. In accordance with previous literature male patients under 65 years old predominate [24].

In a global perspective, the studies considered in this review reported significant PC needs of ESLD patients awaiting LT and some benefits of PC but still an inadequate response to these needs, with challenging barriers to better integration of PC for patients awaiting LT.

Symptoms such as fatigue and sleep disturbance were the most frequent and severe symptoms identified [9, 10] similar to what has been described in a recent meta-analysis [25]. Pain was also reported in one of the included studies [10]. In contrast, breathlessness and sexual dysfunction were not mentioned as they had been in the same meta-analysis [25], with sexual dysfunction not even being evaluated, which suggests that it should also be included in future symptom assessments. Psychological needs were identified but apparently not in the same manner by all professionals, as recommended [11, 13]. A significant burden from psychological symptoms, such as depression, was also identified in more than 50% of ESLD patients included in an Italian survey [26], and anxiety was reported in pretransplantation patients ranging from 27 to 44% [27, 28]. The experience of waiting for a LT has considerable impact on patients [29]. Qualitative studies have described uncertainty as the cornerstone of this psychological process, with very diverse perspectives being reported by patients: some expressed joy and relief and regarded transplantation as an opportunity; others manifested a sense of danger at facing the likelihood of death and of developing cancer during the waiting period [30, 31]. Difficulty coping, loss of trust in physicians and medical, personal and social uncertainties have all been reported [30–32]. LT patients with a coexisting history of substance abuse, in particular, would probably benefit from special attention [33], since this population tends to be threatened by negative attitudes of health care professionals, has a significant risk of noncompliance to treatment and might have special concerns about both symptom management and caregivers' support.

Despite the significant symptom burden, symptom management is still probably suboptimal as suggested by low rates of pain relief [12] and inappropriate professional skills [13]. Adequate medication in ESLD is challenging, since most drugs are metabolized in the liver, thus putting patients at a higher risk of adverse effects. As a result, physicians often resort to less aggressive symptom management. Moreover, physicians may avoid the prescription of opioids to those with a history of substance abuse and often fear the side effects of opioids (e.g., constipation and worsened encephalopathy) [34].

Although there were few studies that directly evaluate the impact of PC in LT patients, most of them identified potential benefits, not only in symptom management [9], but also in goals of care discussions [15], in life-sustaining treatment decisions [19] and even in direct and indirect health costs [19]. Similar results have been reported in patients awaiting other organ transplants [35–37]. There is an inherent difficulty in discussing goals of care and advanced directives with patients pursuing curative therapies, but as suggested by Potosek et al. [34] it is imperative to discuss those and to identify health care proxies, as encephalopathy can impair decision-making. Regarding cost-effectiveness analysis, more studies are required.

Only 2 studies indirectly addressed the quality of life of patients with ESLD [13, 15]. Both favored the PC approach which has a beneficial impact on it. However, robust studies that specifically assess quality of life are essential as one of the cornerstones of the overall PC approach.

The study of Medici et al. [20] reported an improvement of their MELD score during hospice stay, suggesting that this service can potentially provide effective care to terminally ill patients. Although no other study has directly assessed the impact of PC on the prognosis and survival of ESLD patients, it is expected that this might be positive, similarly to studies regarding other medical conditions [38].

Referrals of LT patients to PC seem to be increasing but are still quite low and probably occur only in very late stages of the disease, putting patients at risk for decreased quality of care at the end of life [13, 17–19]. Many barriers have been identified, considering patients, carers, health care professionals and services. The “on the train” perspective hinders the ability of all the interveners to consider a simultaneous approach of PC while awaiting transplantation [14]. Kathpalia et al. [17] considered that these patients represent a unique subgroup of patients with a terminal condition – by virtue of having ESLD – but await the promise of a cure through LT. In this setting, PC, which traditionally has been considered only for

those “at the end of life,” may be perceived – by both the patient and providers alike – as unnecessary and unwelcome. More and appropriate education of health care professionals and training is probably necessary, as suggested in surveys analyzed here [13, 18, 19, 21, 22].

Integration of PC in LT patients seems to be considered essential by all parts [13, 15, 21, 22]. Transplant candidates not only benefit from being provided PC, since they suffer from a terminal condition with significant needs, but also require a complete and complex medical care even when their condition is very advanced [39]. Also, LT patients who are removed from the waiting list often experience withdrawal of specialty care, feelings of abandonment and likely imminent death [34], all of which must be addressed. Development of clinical triggers for PC consultation and effective collaborative approach may clarify better integration [21].

This review was limited by the restricted number of articles included, written only in English, which resulted in a data set that is limited to North American and European ESLD patients that may not take into consideration other relevant realities. Note also that important differences regarding design of the studies may have resulted in significant data heterogeneity, which is beyond the scope of this review since quality assessment was not evaluated.

Conclusions

This review found notable discrepancy between the need for PC and its use in ESLD patients awaiting LT. The belief that transplantation and PC are mutually exclusive still prevails. However, there is increasing evidence that the strategy of providing PC alongside disease-directed therapy while awaiting LT might benefit patients, carers and even the health system. This review indicates some potential areas for developing shared care models. Further research is required, with more robust studies, to better define the optimal strategy of the best way of PC integration for ESLD patients awaiting LT.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Author Contributions

Sara Vieira Silva contributed to the conception of the work, acquisition, analysis and interpretation of the data work, drafted the work and gave the final approval of the version to be published. Elga Freire contributed to the conception of the work, writing of the results, discussion and conclusions, to revising it critically for important intellectual content and gave the final approval of the version to be published. Helena Pessegueiro contributed to the conception of the work, writing of the results, discussion and conclusions, to revising it critically for important intellectual content and gave the final approval of the version to be published.

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