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Position Paper

Unmet needs in hepatology: The guidance of the Italian association for the study of the liver (AISF)

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ABSTRACT

In the last decades, the world of hepatology has widely changed. Although relevant advances have be achieved (e.g. the way toward eradication of hepatitis C virus), many challenges are far to be won. Patients with liver disease continue to face noteworthy barriers to early diagnosis and effective disease management. In response to these tasks, the Italian Association for the Study of the Liver formed a multidisciplinary commission to address the unmet needs of people affected by liver diseases. We analyzed the state of the art of the following consolidated unmet needs: stigma (with particular attention to alcohol-related disease and obesity), specific criticisms of elderly, socioeconomic barriers that patients with liver disorders can face, gender gap in many aspects of liver disease and, finally, the complex issue of quality of life. For each unmet need, we proposed a key-message task and some concrete future perspectives. Preserving a holistic vision and using both multidisciplinary and interdisciplinary method, represent the only effective approach to take on the many unmet needs of patients with liver disorders.

1. Introduction

Liver disease represents a major global health burden, causing over two million deaths per year and accounting for approximately 4% of all deaths worldwide [1]. Mortality due to liver cirrhosis increased by 13% over the past three decades [2], while hepatocellular carcinoma (HCC), the most common primary liver cancer, accounts for 8.3% of all cancer-related deaths worldwide [3]. Despite substantial public health efforts and the introduction of highly effective antiviral therapies for both hepatitis C virus (HCV) and hepatitis B virus (HBV), liver diseases remain the ninth leading cause of death in Western countries. This statistic also reflects an underestimation of the complexity and multidimensional nature of liver disorders [1]. In Italy, as in the rest of Europe, there is a noticeable shift in the etiological distribution of liver diseases, with a decline in cases attributable to alcohol- and HCV infection, alongside a rising prevalence cases due to metabolic dysfunction-associated steatotic liver disease (MASLD) [4,5]. Nevertheless, although alcohol-related cirrhosis cases are currently decreasing, *per capita* alcohol consumption in Europe has been increasing since 2016 especially among young people, raising concerns about the long-term impact of harmful drinking patterns on liver disease burden [6].

The World Health Organization (WHO) defines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [7]. Similarly, well-being is described as a dynamic equilibrium enabling individuals to realize their potential, cope with normal life stresses, work productively, and contribute to their community [8]. This definition highlights the complexity and holistic nature of health, extending far beyond the mere absence of illness to encompass physical, psychological, and social dimensions. Within this framework, unmet needs refer to health and support requirements perceived by patients but inadequately addressed by healthcare services, resulting in distress, diagnostic delays, suboptimal management, and diminished quality of life.

Despite advancements in diagnostic techniques and therapeutic options, patients with liver disease continue to face significant barriers to early diagnosis and effective disease management, stemming from its clinical, social, and systemic complexity. In response to these challenges, the Italian Association for the Study of the Liver (AISF) established a dedicated commission to identify and address the unmet needs of individuals affected by liver diseases.

2. Methods

To produce the present document, several working groups were first formed, each focusing on one of the following thematic areas: stigma, critical issues of old age, socio-economic barriers, gender medicine, quality of life. Each group was expected to include a professional expert in psychological or psychosocial therapies. Each working group conducted a non-systematic review of the scientific literature based on common research methods.

We used the following electronic sources: PubMed, MEDLINE, Google Scholar, Ovid, Scopus, and Web of Science. We considered all papers reporting human-related data (inclusion criteria), excluding articles with unavailable full text, not in the English language, abstracts, book chapters, and articles published before 1990 (exclusion criteria). We then examined supplementary references/articles among manuscripts considered in the first research round.

Each paragraph was organized with the same subsections: state of the art, key points, future perspectives.

A commission of senior expert hepatologists revised the document.

A second-round revision was carried out by some responsible representatives of major Italian Patients Associations (EpaC, Liverpool), by the Italian College of General Practitioners and Primary Care (SIMG) and by an expert sociologist.

3. Stigma

3.1. State of the art

Stigma, in the context of health, can be defined as a process of social impairment that leads to discrimination and loss of status, due to a perceived difference or tag. The World Health Organization (WHO) recognizes stigma as a public health issue, underlying its capacity to worsen mental and physical health outcomes [9]. In people with chronic liver disease, stigma includes negative attitudes, beliefs, and discriminatory behaviours addressed to individuals according to their health condition, impacting on healthcare and patient outcomes. It represents a significant obstacle to the effective management and care of different liver diseases, especially those related to viral hepatitis, alcohol use disorder (AUD), or obesity and MASLD [10–12].

The multiple aspects of stigma are evident throughout the public, personal, and structural levels, each contributing to the overall burden experienced by affected individuals. Alcohol-related liver disease (ALD) and AUD are among the conditions where stigma is particularly pervasive, due to the social imputation of personal responsibility for the development and the persistence of these conditions [13,14]. This public stigma contributes to secrecy surrounding alcohol abuse, delays help-seeking behaviours and increases the overall disease burden. Healthcare professionals are not immune to these biases, with reports of moralizing attitudes

towards ALD patients, negative stereotyping, and potentially influencing the quality of care provided [11,15,16]. Self-stigma, or internalized shame, is another critical dimension where individuals adopt the negative beliefs and attitudes of society towards themselves. This can lead to reluctance to disclose their condition or seek treatment, delaying recognition and referral. Self-stigma can negatively impact treatment adherence and contribute to poorer mental health outcomes, including depression and anxiety, which are already highly prevalent in individuals with AUD [11,13]. Structural stigma refers to systemic policies and practices within healthcare and broader society that unintentionally or intentionally limit opportunities and resources for individuals with ALD and AUD [11]. This can include barriers to mental health services access for individuals with ongoing AUD, inequities in the allocation of limited resources such as liver transplantation (LT), and impairments in health insurance for addiction treatment services. The historical use of stigma terminology in medical settings, such as "alcoholic" "alcoholism" "cirrhosis" and "recidivism" has further entrenched structural stigma by perpetuating negative stereotypes and patient-blaming language [17–19].

Similar stigmatizing dynamics can be experienced by individuals with MASLD, due to lifestyle factors and led by the belief of personal responsibility for this condition. Patients frequently deal with stereotypes, discrimination, and self-blame, with a significant impact on their health-related quality of life they reported more commonly stigmatization related to overweight-obesity (26%) than related to MASLD (8%) [12,20]. Obesity is strictly related with the construct of body image: negative preconceptions that come with not meeting society's bodily ideals, high standards transferred through the culture and the media and body dissatisfaction are particularly prevalent in individuals with obesity [21]; therefore, these factors could play a role on psychological wellbeing. Notably, the evaluation criteria for LT can differ significantly between ALD and MASLD, with a greater emphasis on documented abstinence and "insight" for ALD candidates, potentially reflecting different underlying stigmatizing attitudes [15,17]. Obesity also faces a significant burden of stigma, being often misconstrued as solely a result of personal failings and lack of willpower, leading to public prejudice, self-blame, and discriminatory practices in healthcare and other societal domains [20,22]. This stigma can negatively affect individuals' motivation to adopt healthy behaviours and their willingness to seek medical care, potentially exacerbating the progression of their disease conditions [22]. As already mentioned in case of ALD, the recent adoption of a nomenclature that aims at avoiding stigmatizing language can improve patients' awareness and compliance with health care [19].

The intercurrence of these conditions can further exacerbate the experience of stigma. For example, an individual with obesity and AUD may experience a unique and severe form of stigma due to the co-occurrence of these conditions, perceived as self-inflicted [11]. This highlights the complex interaction of social prejudices and the need for an urgent comprehension of how stigma acts in different health conditions. Moreover, cultural and socioeconomic differences significantly influence the management of liver diseases, affecting patient adherence to treatments and access to healthcare resources. These inequities may hinder effective disease management and worsen outcomes, requiring culturally sensitive approaches in clinical practice [23].

To encourage patient's engagement, public and digital interventions —through media, educational campaigns, and online platforms— on bias and cultural misconceptions could empower patients and contribute to 'destigmatization'. Moreover, educational programs for healthcare professionals could enhance sensitivity to stigma on these groups of patients.

Main drivers of stigma and mitigation factors are summarized in Fig. 1.

3.2. Key points

- Stigma in liver disease, especially ALD and MASLD, manifests across public, personal, and structural levels, deeply impacting patient care and outcomes. Public stigma fosters secrecy and delays in seeking help, while self-stigma leads to shame, reduced treatment adherence, and worsened mental health. Structural stigma is embedded in healthcare systems, with inequities in access to services, insurance, and LT eligibility [10–16].
- Language and terminology (e.g., "alcoholic," "recidivism", "cirrhosis") perpetuate negative stereotypes and patient-blaming narratives [17–19].
- Obesity-related stigma, often linked to body image and perceived personal responsibility, further complicates MASLD management. Co-occurrence of AUD and obesity intensifies stigma, highlighting the need for intersectional approaches [11].
- Cultural and socioeconomic disparities exacerbate stigma's effects, calling for tailored, inclusive interventions [23]. Training healthcare professionals on stigma, especially related to ALD, is essential to improve care and reduce bias.

3.3. Future perspectives

Transplantation of patients with AUD remains a rare example where personal moral judgment may affect the ethical exercise of medicine [24]. Despite the United Network for Organ Sharing (UNOS), International LT Society, the last European Association for the Study of the Liver (EASL) clinical practical guidelines on ALD and on transplantation did not endorse as a formal recommendation the six-month rule of alcohol abstinence before LT, nowadays it is still used and applied, limiting the referral of patients with AUD to LT centres. Clearer and assertive guidelines could overcome this limitation, avoiding any subjectivity in the evaluation of LT eligibility.

Promulgating a dynamic model of individual and social responsibility for AUD, a continuum model of harmful alcohol use, and establishing training on ALD-related stigma for healthcare professionals are strategies to address stigma.

It is urgently necessary to integrate the alcohol addiction unit into the LT Centre, avoiding the frequent separation of addiction services from general healthcare, in order to provide stigma-free prevention [11,25,26]. Overall, a continued shift in healthcare providers' attitudes is needed, away from viewing hazardous alcohol use as a behavioural vice toward AUD as a chronic disease requiring ongoing management [15].

From a practical standpoint, immediate actionable interventions include: 1) Institutionalizing "person-first language" in all clinical documentation to dismantle implicit bias; 2) Establishing co-located joint clinics where Hepatologists and Addiction Specialists evaluate patients simultaneously; and 3) Publicly disclosing standardized transplant eligibility protocols on hospital websites to replace subjective "unwritten rules" (e.g., arbitrary abstinence periods) with transparent, evidence-based criteria.

The lack of transparency in the different LT centres concerning standardized criteria for substance use disorders and periods of required alcohol abstinence is not only an issue for potential patients and their families, but also for healthcare providers. The recent proposal to publicly share online on LT centers' websites a set of standardized criteria regarding LT considerations, eligibility and inclusions in AUD patients could be a useful "destigmatizing tool", although this increased transparency on substance use policies, if stigmatizing, could further perpetuate negative stereotypes [15].

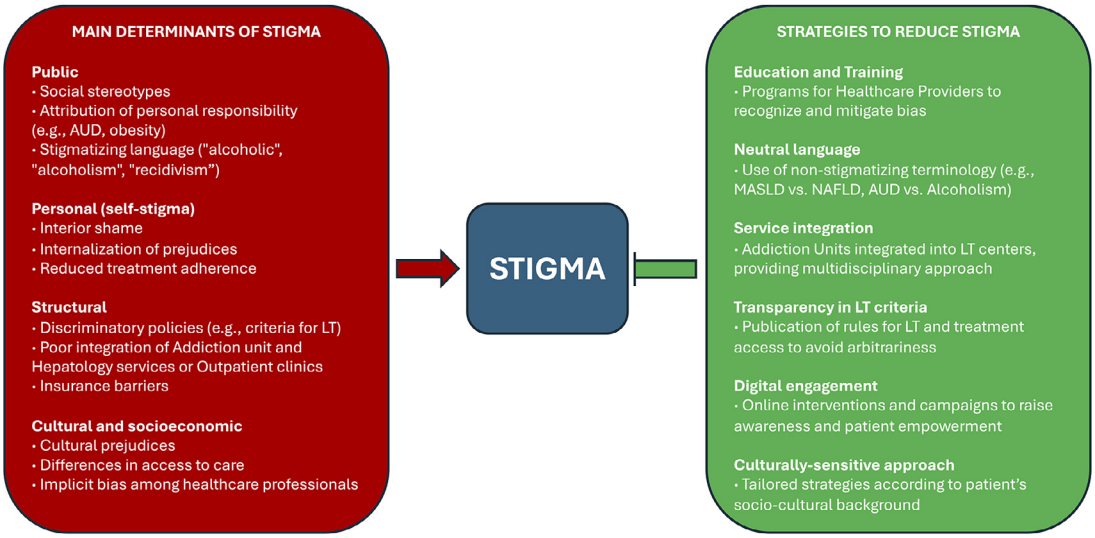

Figure 1. Drivers and mitigation of stigma in subjects with liver diseases. AUD: alcohol use disorder; LT: liver transplant; MASLD: metabolic dysfunction-associated steatotic liver disease; NAFLD: non-alcoholic fatty liver disease.

4. Elderly

4.1. State of the art

Europe has experienced an increase in life expectancy in recent decades, with the number of people aged ≥65 years projected to increase from 90.5 million in 2019 to 129.8 million in 2050, thus posing new challenges for healthcare systems [27]. Despite these changes, the burden of liver diseases in older adults remains under-recognized. During the ageing process, the liver undergoes progressive changes, with liver volume and blood flow known to decrease by 20-40%, and hepatocytes and sinusoids undergo changes that make the liver more susceptible to insults [28–30].

The main differences according to the age in the context of liver disease, are summarized in the Supplementary Figure 1.

Among chronic liver diseases, viral hepatitis remains an important cause in elderly patients [31,32]. In chronic hepatitis B, age-related immune dysfunction and impaired liver regeneration contribute to a higher risk of progression to advanced disease and development of HCC [33]. While the indications for antiviral treatment remain consistent across age groups, age-related factors such as renal function and bone health must guide therapy selection [34]. Entecavir (ETV) and tenofovir alafenamide (TAF) are preferred to tenofovir disoproxil fumarate (TDF) due to their more favourable renal and bone safety profiles [34,35]. In chronic hepatitis C, elderly patients often have long-standing infection and advanced disease, and although these patients have historically been considered difficult-to-treat, direct-acting antivirals (DAAs) have been shown to be as effective and safe in the elderly as in younger cohorts [36–40].

The global epidemiology of liver disease is changing, with a marked increase in MASLD, now emerging as a leading aetiology in elderly patients [41]. Age-related metabolic changes increase the risk of progression to metabolic dysfunction-associated steatohepatitis (MASH) and cirrhosis [42]. From a diagnostic perspective, transient elastography has improved fibrosis assessment, reducing the need for liver biopsies, which are associated with a higher risk of complications in elderly patients [43]. Unfortunately, serum-based scores may not be reliable in this group due to confounding factors [44,45]. Management of MASLD in elderly patients is challenged by limited mobility, frailty and nutritional deficiencies, which can hinder lifestyle modification [46]. Although the US Food and Drug Administration (FDA) recently approved Resmetirom for patients with non-cirrhotic MASH, there is no supporting evidence for patients >75 of age [47]. Glucagon-like Peptide-1 Receptor Agonist (GLP-1 RA) showed promising results for significant weight loss and metabolic improvement in older patients, although slightly higher rates of adverse events have been reported in this population [48,49]. Other more invasive options, such as bariatric surgery, are rarely considered in this group because of the increased perioperative risks [50,51].

ALD is another significant liver condition in elderly patients, which is frequently underestimated [52,53]. The ageing process has been shown to increase susceptibility to alcohol toxicity [30,54]. Psychosocial factors, including loneliness and depression may contribute to significant alcohol consumption [53–55]. In elderly patients, the diagnosis of ALD is frequently made at advanced stages, a finding associated with poorer prognosis [54,55]. Pharmacological treatments for AUD are available, but older adults are rarely included in clinical trials, therefore limiting the availability data on efficacy and safety [56].

In elderly patients, the cumulative burden of chronic liver diseases can lead to HCC, increasingly diagnosed in this population [57,58]. Although age alone should not be a contraindication to treatment for HCC, elderly patients are often undertreated due to frailty, reduced performance status, or perceived ineligibility, despite generally similar therapeutic outcomes as younger patients [59,60]. The high prevalence of comorbidities and sarcopenia further complicates therapeutic decision-making. Nevertheless, curative strategies, including surgical resection and radiofrequency ablation, have demonstrated good efficacy and safety in selected elderly patients [61,62]. Locoregional therapies, like transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), are generally well tolerated, although particular attention must be paid to vascular access and renal function [63,64]. The advent of immunotherapy has expanded systemic treatment options, with available data suggesting comparable efficacy and safety in older and younger patients [65,66]. However, the underrepresentation of elderly patients in clinical trials and the lack of age-specific data remain major limitations.

For selected patients, LT remains the only curative option for end-stage liver disease and HCC. In recent years, the number of elderly candidates has progressively increased: in the US the

proportion of recipients aged ≥65 years rose from 10.2% in 2002 to 17.6% in 2012[67]. Improvements in pre- and post-transplant care have contributed to favourable outcomes in well-selected elderly candidates, whose early survival and complications are comparable to those of younger patients [67,68]. Key factors in patient selection include nutritional status, frailty index, comorbidities and functional status [69]. However, patients aged ≥70 years undergoing LT have demonstrated significantly lower 1- and 5-year survival rates compared to younger recipients, underscoring the importance of careful risk assessment and selection of candidates [70]. On the donor side, with meticulous donor-recipient matching and rigorous donor selection criteria, favourable outcomes can also be achieved using grafts from donors aged ≥65. Several studies have shown that rates of post-transplant complications, including biliary and vascular complications, and recipients survival do not differ according to donor age [71,72]. These evolving dynamics underscore the necessity for refined selection strategies and more data focused on transplant outcomes in older populations.

4.2. Key points

- Elderly patients are increasingly affected by chronic liver diseases, yet they remain underrepresented in clinical trials, limiting age-specific evidence and tailored therapeutic guidance.
- Comorbidities, frailty, sarcopenia, and reduced physiological reserve often affect diagnostic accuracy, therapeutic decision-making, and treatment adherence.
- Lifestyle interventions remain the cornerstone of care for MASLD but are difficult to implement in older populations. Pharmacological and interventional strategies also lack tailored guidelines for this age group.
- LT can be successful in selected older patients, but careful pre-transplant assessment and individualized risk stratification are essential.
- Social isolation, loneliness and depression are common in older adults and contribute to the risk of chronic liver diseases such as MASLD and ALD, supporting the need for preventive interventions.
- Future priorities include the development of age-adapted care pathways, wider inclusion in clinical trials, engagement of family/caregivers, improved patient–hospital connectivity and integrated multidisciplinary models to ensure equitable and evidence-based care for older adults with liver disease.

4.3. Future perspectives

As the global population continues to age, managing liver diseases, including MASLD, ALD and HCC, in older adults is becoming an increasingly common clinical challenge [27]. Elderly have unique biological, functional and psychosocial characteristics that influence diagnosis, treatment decisions and outcomes. Despite this, they remain underrepresented in clinical trials, leading to treatment uncertainty in real-life clinical practice. Although liver transplantation is feasible in selected older adults, clear criteria and specific risk stratification tools for this age group are still lacking [70,73]. Future efforts should focus on increasing the number of elderly patients enrolled in prospective clinical trials, incorporating geriatric assessment tools into hepatology practice, and designing tailored care pathways that consider frailty, comorbidities, polypharmacy, functional reserve and social vulnerability. The use of digital health and telemedicine solutions can also help overcome mobility limitations and support continuous follow-up of frail patients [74]. A multidisciplinary and age-sensitive approach involving hepatologists, caregiver, geriatricians and oncologist is essential not only to improve care, but also to ensure that age is not a barrier to effective and equitable treatment.

The main analyzed issues are reported in the Table 1.

5. Socioeconomics barriers

5.1. State of the art

Socioeconomic factors have recently gained increasing attention in clinical research and public health analyses for their pivotal role in liver diseases [75]. Indeed, while significant advances have been made in hepatology treatments and diagnostics, uneven resource distribution can undermine equitable access to care across national and regional healthcare systems [76]. Addressing these disparities is particularly urgent in light of the major shift in the aetiology of cirrhosis, with alcoholic and metabolic forms now accounting for 60–70% of all cases [5]. These aetiologies require diversified therapeutic approaches and are strongly influenced by socioeconomic determinants such as lifestyle, prevention, and early intervention.

Current evidence indicates that individuals with lower socioeconomic status face higher rates of liver-related morbidity and mortality [77]. This is most evident in conditions including ALD [78], MASLD [79], viral hepatitis [80,81], and their complications such as HCC [82,83], where both exposure to risk factors and access to preventive measures can be hindered by socio-economic constraints. Notably, barriers extend beyond low income alone, encompassing travel challenges to referral centres, potential income loss from work absences, and the difficulties of adhering to healthy lifestyles under financial or housing limitations. Family dynamics also play a critical role: the absence of adequate familial support or caregiving substantially hinders disease management and compromises treatment adherence. Finally, work life can also be affected by liver disease, resulting in lower employment rates, increased absenteeism, and reduced productivity while at work (presenteeism) [84–87]. Although improvements are seen after liver transplantation, full reintegration into the workforce is often not achieved [88].

In Italy, despite universal healthcare coverage, there are marked regional and rural/urban variations in resource allocation and specialized care availability [89,90]. Behavioural habits and socioeconomic conditions differ across the country, contributing to heterogeneous geographical patterns of chronic liver disease, with ALD more frequent in northern/central areas and viral hepatitis more common in the southern regions and main islands [91]. Historical data on more than 35 million Italian individuals found chronic liver diseases to be among the top causes of death associated with the greatest socio-economic disparities [92]. Migrants, in particular, face multiple obstacles beyond economic limitations [93], including language barriers and cultural or legal hurdles, which can delay diagnoses and lead to suboptimal treatments [94]. Supporting this, a recent prospective study in Tuscany showed higher HBV/HCV prevalence among marginalized populations than in the general population, with HBV being more prevalent in economic migrants/refugees and HCV among Italian individuals experiencing extreme marginalization [95]. Migrants who are HBsAg-positive also differ significantly from Italian carriers in demographic, serological, and virological profiles, as well as in access to antiviral treatment [96].

Socioeconomic constraints affect the ability to adopt lifestyle modifications crucial for liver health. Low income and unstable employment have been linked to poorer adherence to the Mediterranean diet [97–99], a protective factor against MASLD, and to more harmful alcohol use in both native and migrant populations [100,101]. Furthermore, Italy's aging population—often presenting multiple comorbidities and disabilities—requires complex, integrated care that can be restricted by socioeconomic limitations.

Table 1
Overview of key challenges, impact, and future directions in the management of chronic liver diseases in older adults.

Liver Disease	Challenges and current limitations	Impact on Outcomes	Potential Future Directions
MASLD	- Frailty and sarcopenia - Cognitive impairment - Lack of validated geriatric-specific non-invasive tests - Limited inclusion in clinical trials	- Poor adherence to lifestyle modifications - Delayed diagnosis	- Tailored lifestyle interventions - Inclusion in clinical trials - Integration of digital health tools for monitoring and support - Multidisciplinary care involving professionals, caregivers, and motivators
ALD	- Psychosocial vulnerability - Stigma and reluctance to seek help - Limited data on pharmacologic therapies	- Late-stage presentation - Underdiagnosis	- Psychosocial screening - Multidisciplinary approach with addiction specialists, geriatricians and patient association self-help groups
HCC	- Comorbidities - Frailty and sarcopenia - Underrepresentation in clinical trials - Limited geriatric-specific data on immunotherapy and combination treatments	- Undertreatment - Lower access to curative therapies	- Geriatric-informed clinical trials and treatment pathways - Validation of frailty scores in treatment decision-making - Use of AI tools for patient stratification and personalized care
Liver Transplant	- Increased surgical risk - Comorbidities - Reduced physiological reserve - Lack of social support - Lack of standardized criteria for eligibility	- Reduced access to transplant - Higher early mortality	- Multidimensional geriatric assessment - Selective donor-recipient matching - Harmonized criteria for elderly transplant evaluation

MASLD: metabolic dysfunction-associated steatotic liver disease, ALD: Alcohol-Related Liver Disease; HCC: Hepatocellular Carcinoma.

Finally, the COVID-19 pandemic has exacerbated existing inequalities: disruptions to routine screening programs and hepatology services [102] have led to delayed diagnoses and poorer outcomes in socioeconomically disadvantaged groups.

5.2. Key points

- Inequalities in healthcare resources for liver disease patients arise from both resource availability and patients' ability to access and utilize them effectively.
- Resource availability varies across Italian regions, with disparities in screening, diagnosis, and treatment due to differences in essential care levels and urban-rural divides. This creates a "postcode lottery," where care quality depends on geographic location, with urban centres offering specialized services and rural patients facing limited access and longer travel times.
- Patients' capacity to use available resources is hindered by low health literacy, limited education, and language barriers.
- Economic constraints impede regular medical visits and necessary lifestyle modifications for conditions such as MASLD and MetALD.
- Vulnerable populations experience additional barriers, including differing prevalence of liver disease, transportation issues, work conflicts, and cultural factors affecting healthcare-seeking behaviours.
- An effective approach requires multidisciplinary strategies addressing both clinical and socioeconomic factors, often overlooked by healthcare providers focusing solely on treatment.

Main key points are summarized in the Fig. 2

5.3. Future perspectives

To address the disparities in healthcare resources for liver disease patients, several strategic perspectives are essential. Strengthening healthcare infrastructure and access must be a priority, ensuring uniform availability of screening and early diagnosis services across all regions, including underserved rural areas and urban peripheries. This includes reinforcing the role of primary care in both prevention and ongoing monitoring, as well as improving integrated care models tailored to chronic liver diseases. Equitable access to innovative treatments should be guaranteed nationwide by advocating for their inclusion in the Essential Levels of Care (LEA). Dedicated care pathways should be established for vulnerable populations, and telehealth services expanded to bridge the geographic gaps between urban and rural settings. Moreover, comprehensive patient management requires addressing non-clinical factors through a multidisciplinary approach that encompasses social and economic determinants of health.

Institutional collaboration plays a crucial role in these efforts. Dedicated training programs focusing on social determinants of health for hepatology residents and healthcare professionals can enhance awareness and competence. Strengthening communication between scientific societies and political institutions will facilitate policy alignment and resource allocation. Cross-regional partnerships among healthcare institutions can foster resource sharing and expertise exchange, while collaboration with patient advocacy groups and local health services is vital for raising public awareness and driving policy changes aimed at reducing health inequities.

Regarding patient capabilities and resource distribution, interventions must simultaneously promote equal access opportunities and empower individuals to manage their conditions effectively, considering barriers such as health literacy and economic constraints. To ensure progress, continuous monitoring and evaluation of equity in healthcare access and outcomes are necessary. This includes collecting socio-economic stratified data—covering variables like income, education, and ethnicity—to identify disparities. It is crucial to collect these indicators both at the individual and area-level indicators, to identify micro, meso, and macro deprivation factors, and to avoid ecological fallacies. Detailed analysis of health outcomes, including treatment success and complication rates, helps reveal inequities in care quality. Developing robust methodologies to assess the impact of equity-focused interventions enables targeted efforts towards vulnerable groups. Maintaining progress requires ongoing monitoring and iterative adjustment of strategies. Collaboration among healthcare providers, policymakers, and community organizations is fundamental to creating comprehensive solutions that effectively address disparities in liver disease care.

Finally, education, prevention, and screening programs must be expanded and tailored to community needs, starting from school-based education and reaching the public through various media channels. Organizing outreach initiatives can improve health

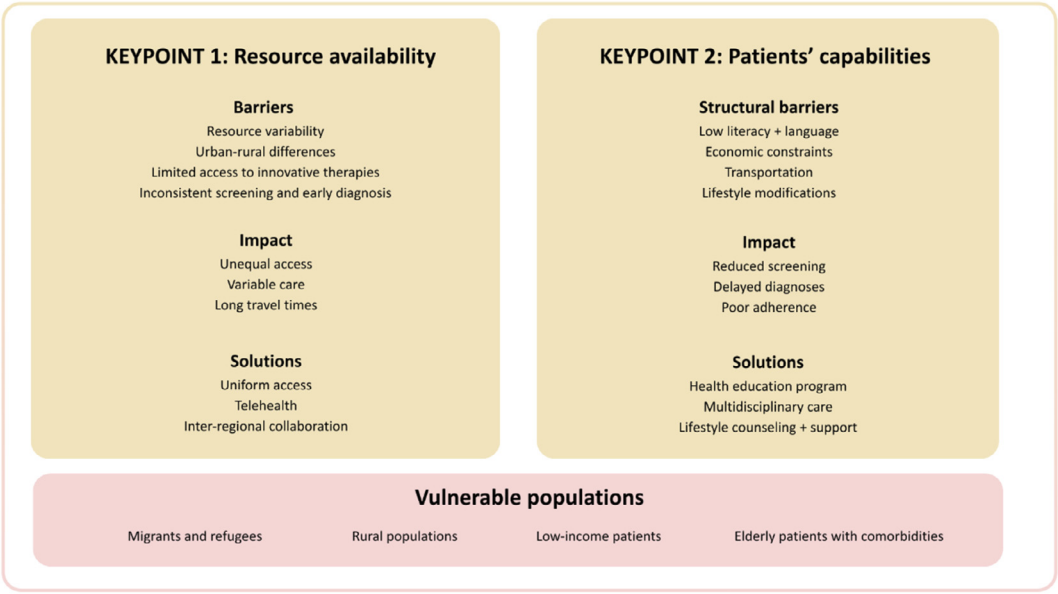

Figure 2. The complex issues related to socio-economics barriers in the context of liver diseases.

literacy and encourage screening participation, especially among high-risk groups such as individuals with a history of alcohol abuse or obesity. Nutritional counselling and support programs are also critical components, aiding patients in managing diet-related factors essential for liver health.

6. Gender inequalities

6.1. State of the art

Biological sex plays a major role in the development of health and disease, including liver diseases [103]. The liver itself is a sexually dimorphic organ, exhibiting significant structural and functional differences between males and females [104]. These differences influence the epidemiology, clinical presentation, natural history, and response to treatment of many acute and chronic liver diseases, which vary significantly between the sexes. These disparities, summarized in the Fig. 3, can be attributed to a range of sex-specific factors, including genetic, hormonal, and immune-related influences [105]. For example, sex hormones like estrogens and androgens directly impact liver metabolism, immune function, and cellular repair mechanisms. Animal models have shown that estrogen has a protective effect against fibrogenesis and inflammation, whereas androgens may contribute to liver injury and tumor development in certain contexts [106–108]. This explains why globally females show a better prognosis than males. In fact, in 2019, the frequency of incident cases, deaths, and disability-adjusted life-years due to cirrhosis was 1,206,125; 969,068; and 31,781,079 in males *versus* 845,429; 502,944; and 14,408,336 in females, respectively. However, it is important to underline that, from 2010 to 2019, frequency of cirrhosis-related deaths raised by 9% in males and 12% in females [109].

This understanding has led to increased efforts towards a personalized, sex-driven approach to the study and management of liver diseases, which would consider these sex-specific differences. A growing body of research emphasizes the importance of tailoring diagnostic and treatment strategies based on biological sex [110–113].

It is essential, however, to distinguish between biological sex and gender, the latter of which encompasses a broader range of physical, psychological, social, and cultural elements. Gender roles and identities, healthcare access, and social expectations can all influence how diseases are perceived, reported, and treated. However, research on this topic is not yet well developed. While both sex and gender contribute to health outcomes, this discussion centers on the impact of biological sex. Therefore, the term 'sex' will be used throughout this article as shorthand for biological sex, acknowledging that sex and gender are distinct.

The influence of biological sex is particularly evident in certain liver diseases. Autoimmune liver diseases, for instance, show a clear female dominance, with women comprising up to 90% of primary biliary cholangitis (PBC) cases and 70–90% of autoimmune hepatitis (AIH) cases [114]. This is thought to be due to a stronger immune response in women, driven by estrogen and other sex hormones that influence immune cell activation and antibody production. Conversely, while men are less frequently affected, they tend to experience more severe disease progression, with higher incidences of fibrosis, resistance to treatment, and complications such as cirrhosis or HCC [115].

In real-world practice, sex-specific considerations in clinical decision-making and treatment access are often overlooked. Two major problems persist: the under-representation of women and men in clinical trial populations, and the frequent absence of sex-stratified analyses. In a review of 107 U.S. clinical trials, 72% did not report results by sex [116]. This gap limits clinicians' ability to counsel patients on prognosis and increases the risk of adverse drug events, given known sex differences in drug distribution and clearance. For example, women receiving drugs approved through male-dominated trials experienced higher rates of adverse events due to increased plasma drug concentrations [117]. A study of 20,020 U.S. clinical trials (2000–2020) found substantial sex disparities in enrolment [118]. Pediatric, cardiology, and infectious-disease trials had particularly low female participation (adjusted relative differences: −20.5%, −18.7%, and −18.5%, respectively). Even in gastroenterology, women were under-represented by 12.8%, despite their high burden of gastrointestinal disease. Such imbalances mean trial populations often fail to reflect real-world patients. Because clinical trials provide privileged access to innovative therapies unequal enrolment is both unfair and unethical. Sex also influences therapeutic responses. In autoimmune hepatitis, men have higher relapse rates, whereas women are more likely to achieve ALT normalization at 6 and 12 months. In primary biliary

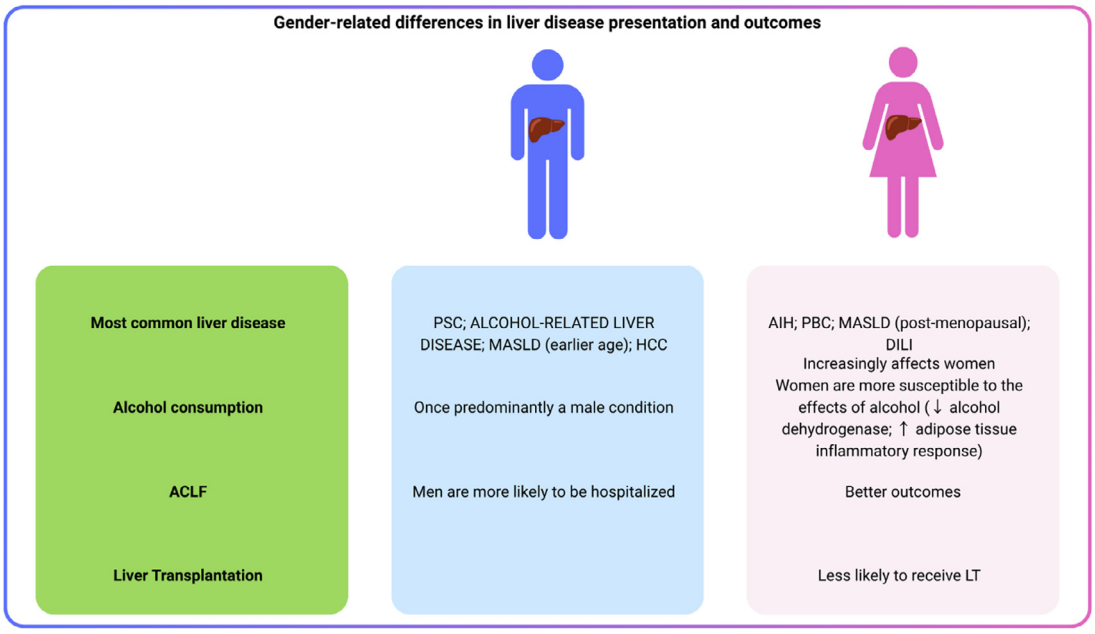

Figure 3. Gender-related differences in liver disease. ACLF: acute on chronic liver failure, MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease, HCC: Hepatocellular Carcinoma, AIH: autoimmune hepatitis, PBC: primary biliary cholangitis, DILI: Drug-induced liver injury, LT: liver transplantation.

cholangitis, men show higher ALP levels and poorer biochemical responses to UDCA, increasing their risk of progression and decompensation. In cirrhosis with portal hypertension, responses to NSBBs appear similar across sexes [119], but with new therapies emerging [120], potential sex-related differences in pharmacokinetics and pharmacodynamics should be further considered.

Drug-induced liver injury (DILI) further underscores how sex-based biological differences can affect drug metabolism and responses [121]. Women are more vulnerable to DILI, particularly when an immune-mediated mechanism is involved. Factors such as slower liver drug metabolism, variations in cytochrome P450 enzyme activity, and differences in immune surveillance contribute to this increased risk [122]. Estrogens may offer some protection in pre-menopausal women, but post-menopausal individuals tend to experience a rise in DILI rates, suggesting hormonal influences on liver resilience [123]. Despite this, most drug trials continue to lack sufficient sex-specific safety data, which hinders clinicians' ability to predict and manage adverse drug effects [103].

ALD, once predominantly a male condition, is increasingly affecting women, especially following changes in social norms and rising alcohol consumption among women post-COVID-19 [110,124]. Women are more susceptible to alcohol's harmful effects due to biological factors like lower gastric alcohol dehydrogenase activity and reduced body water content, which leads to higher blood alcohol levels after equivalent consumption [125]. Additionally, women's adipose tissue shows a heightened inflammatory response to alcohol, further increasing the risk of liver damage [126]. In MASLD, men are typically diagnosed at an earlier age, while post-menopausal women experience a marked increase in incidence, corresponding with declining estrogen levels [111]. These hormonal changes affect insulin resistance, fat distribution, and muscle mass, which influence disease progression [127,128]. Despite these sex-specific differences, there is a lack of clear guidelines for screening, monitoring, or managing MASLD, a growing concern as the incidence of MASLD continues to rise. Similarly, HCC – which usually arises on top of alcohol and MASH related cirrhosis – predominantly affects men, with androgen receptor activation linked to tumor development, while estrogens appear to offer protective effects [113]. However, women are often diagnosed at later stages and less frequently participate in clinical trials, suggesting gaps in screening and research inclusivity, as well as a potential reluctance to join trials, that adversely affect female patients [129].

Acute-on-chronic liver failure (ACLF) is a characterized by acute decompensation of cirrhosis, extra-hepatic organ failures, and high risk of short-term mortality. ACLF presents differently based on sex, with men more likely to be hospitalized, but women tending to have better outcomes during the initial stages, possibly due to immune modulation influenced by sex hormones [130,131]. Nevertheless, current prognostic models do not incorporate sex as a factor, limiting their predictive accuracy and potentially affecting treatment decisions. LT, the only curative treatment for patients with ACLF, also reflects significant sex-based inequities, with women less likely to receive transplants, despite having similar post-transplant survival rates as men. Factors such as body size impacting Model for End-stage Liver Disease (MELD) scoring, limited access to living donors, and potential clinical biases contribute to this disparity. As recently shown in an Italian cohort [130], although post-transplant survival rates are similar, women are less likely to receive transplants due to factors like smaller body size impacting MELD scoring [132], limited access to living donors, and possible biases in clinical evaluations [133]. These differences are particularly pronounced in HCC patients, where women are more frequently delisted despite having similar disease burdens as men.

It bears noting that chronic liver disease can be associated with depression and psychological disorders. Depression is more prevalent in women than in men, with women facing a 2- to 3-fold higher risk of developing major or dysthymic disorders. WHO estimates show a global prevalence of 25% in women compared to 12% in men [134]. In Italy, the lifetime prevalence of major depression and dysthymia is 11.2%, with a female-to-male ratio of 2:1. This gender disparity may stem from genetic, hormonal, and life-phase-specific factors, such as postpartum depression (10–12% incidence), premenstrual dysphoric disorder (1.8%), and menopause-related mood changes. Access to care is often hindered by psychiatric comorbidities like depression. Depressed individuals may downplay physical symptoms, leading to delayed diagnoses, poor adherence to treatment, and worse outcomes. They often struggle

with motivation, resulting in inconsistent medication use and neglect of health-promoting behaviours. Core depressive symptoms—such as apathy and anhedonia—can further impair their ability to follow medical advice, increasing the risk of unhealthy behaviors, including substance and alcohol abuse [135].

Finally, there are also lesser-understood conditions in liver disease where sex seems to play a role, such as vascular liver diseases like hepatic and portal vein thrombosis, porto-sinusoidal vascular disorder (PSVD), and hereditary hemorrhagic telangiectasia. The latter is more prevalent and severe in women, while evidence on sex differences in other vascular liver diseases remains inconclusive. Furthermore, conflicting data exist on the association between sex and the risk of non-cirrhotic portal vein thrombosis, though morbidity and mortality from thrombotic events appear comparable between the sexes [136].

In conclusion, biological sex significantly influences the development, progression, and treatment of various liver diseases. Gaining a deeper understanding of the impact of sex on liver disease pathophysiology, clinical manifestations, and treatment responses is critical to improving patient management, advancing therapeutic strategies, and ultimately reducing liver-related morbidity and mortality.

6.2. Key points

- The liver shows structural and functional differences between males and females, affecting immune responses, metabolism, and disease progression.
- Women are significantly more affected by autoimmune liver diseases such as PBC and AIH, likely due to estrogenic-driven immune modulation.
- Women, particularly those who are post-menopausal, are more susceptible to DILI due to variations in drug metabolism and immune surveillance.
- Increased alcohol consumption among women has resulted in a rise in ALD cases in females, who are biologically more vulnerable to the effects of alcohol.
- Despite achieving equal or better outcomes, women are less likely to receive liver transplants due to MELD scoring biases, smaller body size, and limited access to living donors.

6.3. Future perspectives

Biological sex plays a critical role in the development, progression, and treatment outcomes of many acute and chronic liver diseases. However, persistent sex disparities continue to hinder timely diagnosis, equitable access to care, and balanced representation in clinical research. To address these challenges, future efforts must consistently incorporate sex as a key variable in prognostic models and clinical trials, revise LT criteria to eliminate systemic bias, and establish sex-specific guidelines for managing liver conditions. Additionally, targeted education and awareness initiatives for both healthcare providers and individuals with liver disease are essential to promote a more inclusive, personalized approach to care. Only through a comprehensive, equity-driven strategy we will be able to close the “sex gap” in hepatology, thus improving outcomes for all individuals in need.

7. Physical and psychosocial determinants of health-related quality of life

7.1. State of the art

Liver disease profoundly affects Health-Related Quality of Life (HRQoL), even in early stages and regardless of aetiology [137–147]. While disease progression is a major driver of HRQoL impairment [137–144], numerous symptoms and psychosocial factors play a critical role independently of severity. Among clinical determinants, chronic pain [148–151], cramps [152], sleep disturbance [153,154], sexual dysfunction [155,156], malnutrition, frailty [146,157,158], pruritus [159], fatigue and comorbidities [141,160] consistently correlate with reduced HRQoL. Medication burden and treatment side effects further exacerbate this impact [149,161–164]. Portal hypertension-related complications, such as ascites and hepatic encephalopathy (HE), can be particularly detrimental to patients [162,164–172]. Ascites contributes to fatigue, pain, and digestive symptoms, often signalling disease progression and evoking fear of mortality. HE, including covert forms, disrupts cognition and sleep, with overt episodes often perceived as traumatic due to falls and loss of autonomy [173,174]. However, treatment (e.g., diuretics, Transjugular intrahepatic portosystemic shunt) offers patients a sense of hope [175]. Disease aetiology modulates the pattern of HRQoL impairment. Alcohol-related, viral, autoimmune, metabolic, and cholestatic liver diseases each present distinct burdens (see Table 1). Patients with AIH often report fatigue and anxiety [176], while those with PBC experience severe pruritus and depression [177]. MASLD patients, burdened by comorbidities and stigma related to weight and diet, show the lowest HRQoL scores [178,179].

The psychological and social impact of liver disease is substantial. Anxiety, depression, sadness, and difficulty in accepting their condition are commonly reported, especially in rare or less intuitive diagnoses [153,164,180–187]. The gap in patient education about disease trajectory, lifestyle management, and therapeutic options remains a persistent unmet need [187–190]. Many patients feel unsupported in implementing behavioural changes and report inadequate communication on prognosis and end-of-life preferences [191]. On the other hand, clinicians often encounter resistance to lifestyle changes and adherence to treatment, even when communication seems clear, complete, and thorough. This issue relates to the broader and complex matter of communication in healthcare, highlighting the importance for clinicians to use good communication strategies and to consider the factors that influence patients’ readiness for change and motivation to adopt more healthy lifestyles.

Several modifiable factors can improve HRQoL. Trust in treatment, supportive physician relationships, and care in transplant centres are positive contributors [192]. Exercise and nutritional support can alleviate sarcopenia and fatigue, while pharmacological treatment of HE enhances cognitive performance and sleep quality [193]. Additionally, structured patient education and psychological counselling have shown a positive impact on patients’ ability to cope with disease burden and improve overall HRQoL [194].

However, non-clinical determinants - such as low education, income, social support, and gender disparities - further compound HRQoL decline [195]. Tailored interventions across disease stages, from chronic liver disease to decompensated cirrhosis, are crucial. Importantly, improving disease literacy and reducing stigma through greater public awareness may relieve much of the psychosocial burden experienced by patients.

The analysis of the literature reveals inconsistent results regarding the correlation between specific liver diseases and dimensions of HRQoL. This can likely be attributed to the variability of multiple factors, such as the sample size and patients characteristics in the studies, the methodological quality and the heterogeneity of the questionnaires used [137–145].

The tools currently used to assess HRQoL in patients with liver disease fall into two categories:

- Generic quality of life questionnaires, such as the Short Form (SF-6D, SF-8, SF-12, SF-36), European Quality of Life (EQ-5D), Pediatric Quality of Life Inventory (PedsQL), Sickness Impact Profile (SIP), Nottingham Health Profile (NHP) and others.

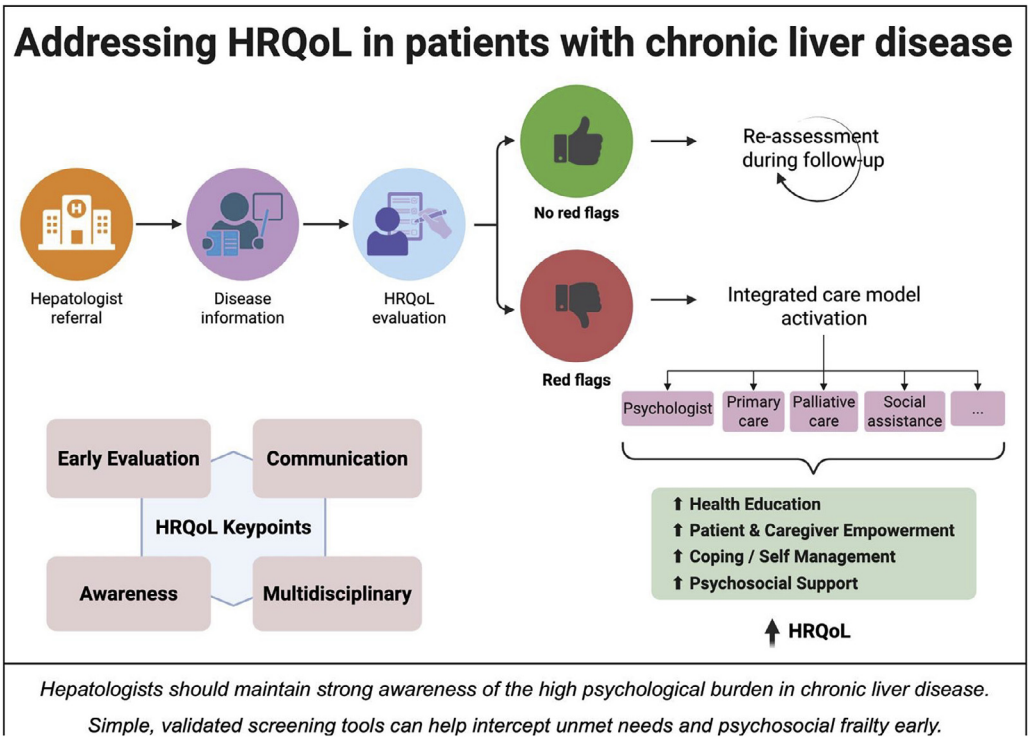

Figure 4. Integrated model centered on patient quality of life in the management of liver disease. This approach enables the timely identification of physical, psychological, and social needs, activating targeted interventions to improve the overall well-being of the patient throughout the disease course through integrated care model activation. HRQoL= Health-Related Quality of Life.

- Liver disease-specific questionnaires, such as the Chronic Liver Disease Questionnaire (CLDQ), Liver Disease Quality of Life (LDQOL), Liver Disease Symptom Index 2.0 (LDSI 2.0), Primary Biliary Cholangitis Questionnaire (PBC), Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) and others.

Among the issues emerging from the literature, very important is the risk of underestimating symptoms and liver disease itself during the early stages of the illness. Even if certain diseases more clearly reveal psychological distress in patients at specific stages nevertheless, such issues are present throughout the entire disease trajectory and should be addressed from the beginning. In fact, vulnerability to developing emotional distress and/or psychological disorders appears to be more closely associated with patients' negative or maladaptive coping styles—that is, the strategies they adopt to deal with the illness experience—than with specific diseases or stages of illness.

An ideal model for identifying and addressing the needs of patients with liver disease should go beyond clinical management and adopt a holistic, patient-centred framework. This approach integrates physical, psychological, and social dimensions of care, with the goal of enhancing HRQoL throughout the illness trajectory. Early and structured HRQoL assessment using rapid tools (e.g., SF-12, SF-36) should be embedded into routine hepatology care. This enables timely identification of distress, functional limitations, or unmet informational needs, allowing targeted integrated care model activation (Figure 4).

Enhancing quality of life should be a clinical priority. Managing patient-reported symptoms and providing nutritional and exercise support are key elements of care. Equally, reducing polypharmacy and tailoring treatments to minimize side effects are essential to improving HRQoL. Furthermore, health education is a key lever of empowerment. Patients and caregivers need clear, repeated, and personalized communication about disease progression, therapeutic options, and self-management strategies. Education should start at diagnosis and evolve over time, with a focus on behavioural change, treatment adherence, and understanding prognosis.

Empowerment of patients and caregivers involves engaging them actively in decision-making processes. Shared care approaches and motivational interviewing promote autonomy and resilience. Yet, a comprehensive model should also ensure access to psychosocial support through defined referral pathways to mental health professionals, psychologists, and social workers. Group or peer support programs can further improve emotional well-being and reduce stigma.

An integrated care model should include close collaboration with both primary care and palliative services to guarantee continuity, especially in advanced stages. Primary care providers are essential in reinforcing lifestyle modifications and managing comorbidities. Palliative care, introduced early, should focus on symptom management, goal-of-care discussions, and psychological support, long before end-of-life.

7.2. Key points

- HRQoL is profoundly affected by any liver disease and requires a standardized clinical assessment based on generic and liver-disease specific questionnaires.
- The attention to patient-reported symptoms, an adequate nutritional and exercise support along with reduction of polypharmacy are the main areas of intervention.
- Educational programs directed to patient and care givers may warrant behavioural changes, treatment adherence and understanding prognosis.
- The passage from a disease-centred to a person-centred model of care represents a paradigmatic shift to translate clinical advances into meaningful improvements in quality of life.

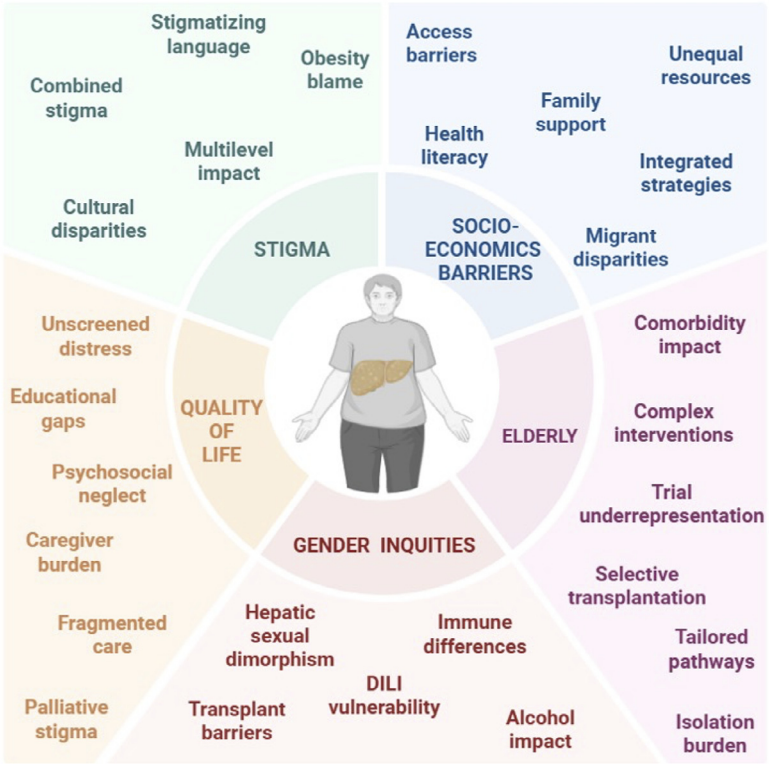

Figure 5. Key points of the main areas referring to unmet needs in the context of liver disorders. DILI: Drug-induced liver injury.

7.3. Future perspectives

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Finally, several barriers limiting HRQoL for liver disease patients and their caregivers should be addressed, including faster referrals to appropriate facilities, streamlined pathways for patients with limiting symptoms, easier access to hospital-dispensed medications, reduced bureaucracy, and greater involvement of primary care physicians.

8. Conclusions

The present document addresses the main issues that represent the unmet needs of patients with reference to liver diseases. The main key points that have emerged are summarized in Figure 5. In addition to the issues partially addressed in the current literature, patients with liver disease continue to face bureaucratic, administrative, and structural challenges that complicate their care pathways. Greater institutional recognition and involvement of caregivers, together with dedicated information and prevention campaigns, as well as the simplification of administrative procedures—including through digitalization—should be actively considered and promoted by health authorities.

The tumultuous epidemiological and technological changes of recent decades, along with increasing economic, social and environmental sustainability challenges, have made the unmet needs progressively more impactful. The health institutions, in concert and in alliance with the various professionals involved in care and scientific research, must collaborate to fill the various gaps that exist between assistance and patient needs. In this context, the central role that nurses could assume as a bridge between patients and other professionals represents an issue that should be further explored and valued at the national level.

Unmet needs vary significantly across geographical and cultural contexts. At the continental level, scientific societies have approached these challenges through different strategies and

initiatives. The European Association for the Study of the Liver (EASL) has recently issued a policy statement on stigma and discrimination [196]. EASL also emphasizes patient empowerment by providing tailored educational materials and communication tools through its dedicated platforms [10,197]. Similarly, the American Association for the Study of Liver Diseases (AASLD) highlights the relevance of unmet needs both within its disease-specific guidelines [198,199] and through dedicated sessions at its annual congress, as well as patient-focused resources available on its website [200]. The Asian Pacific Association for the Study of the Liver (APASL) acknowledges some of these unmet needs—particularly those related to stigma—mainly through clinical research, although clear policy statements or structured positions on the topic are still lacking [201].

This study has some clear limitations. First, it was not developed following the methodology of the Guideline. This decision was made because as the available studies on the topics discussed often lack the robustness of randomized controlled study. Therefore, we believe there are no prerequisites for producing a Guideline, at least for the moment. Furthermore, the literature review was non-systematic. Finally, not all the unmet needs were explored and addressed. For example, the issue related to health and environmental sustainability certainly represents a growing problem and will deserve future dedicated studies.

Despite this, the present work represents an important multidisciplinary initiative that has engaged the main actors involved in the cure of liver diseases with a not only medical but also psychological and social point of view. Finally, we believe that the involvement of patient Associations has been essential.

In conclusion, maintaining a holistic vision and having a multidisciplinary and interdisciplinary approach represent the only effective way to pursue the aforementioned objectives. The compass of this action should not be solely on disease treatment or prevention, but at the overall well-being of the patient, with a view to protecting both the individual and the broader community.

Declaration of competing interest

We declare that none of the authors of the manuscript entitled “Unmet needs in Hepatology: the Guidance of the Italian Association for the Study of the Liver (AISF)” show any conflict of interest.

Acknowledgments

The present Guidance is dedicated to the memory of Ivan Gardini, President of EpaC and co-author.

Ivan dedicated his life in EPAC to face the unmet needs of patients, deeply inspiring us and the present document.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.12.016.

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