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## Financial Burden in Adults with Chronic Liver Disease: A Scoping Review

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### Abstract

**Background & Aims:** The economic burden of chronic liver disease is rising, however the financial impact of chronic liver disease on patients and families has been underexplored. We performed a scoping review to identify studies examining financial burden (patient/family healthcare expenditures), financial distress (material, behavioral, and psychological consequences of financial burden), and financial toxicity (adverse health outcomes of financial distress) experienced by patients with chronic liver disease and their families.

**Methods:** We searched Medline, Embase, Cochrane Library, and the Web of Science online databases for articles published since the introduction of the Model for End-Stage Liver Disease score for liver transplant allocation in February 2002 until July 2021. Final searches were conducted between June and July 2021. Studies were included if they examined the prevalence or impact of financial burden or distress among patients with chronic liver disease and/or their caregivers.

**Results:** A total of 19 observational studies met inclusion criteria involving 24,549 patients and 276 caregivers across 5 countries. High rates of financial burden and distress were reported within the study populations, particularly among patients with hepatic encephalopathy, hepatocellular carcinoma, and liver transplant recipients. Financial burden and distress were associated with

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**Analysis and interpretation of data:** Ufere, Satapathy, Serper

**Drafting of the manuscript:** Ufere, Satapathy

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increased pre- and post-transplant healthcare utilization and poor health-related quality of life as well as caregiver burden, depression, and anxiety. None of the included studies evaluated interventions to alleviate financial burden and distress.

**Conclusions:** Observational evidence supports the finding that financial burden and distress are underrecognized but highly prevalent among patients with chronic liver disease and their caregivers and are associated with poor health outcomes. There is a critical need for interventions to mitigate financial burden and distress and reduce financial toxicity in chronic liver disease care.

### Keywords

Financial distress; financial toxicity; financial hardship; end-stage liver disease; cirrhosis; palliative hepatology

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## INTRODUCTION:

The global burden of chronic liver disease is rising, affecting over 1.5 billion individuals worldwide.<sup>1</sup> In Europe, liver disease is now the second leading cause of years of working life lost, following ischemic heart disease.<sup>2</sup> In the United States, there have been rising rates of cirrhosis-related hospitalizations and consequent annual healthcare costs over the past two decades, outpacing those for patients with congestive heart failure.<sup>3,4</sup>

Despite the growing recognition of the increasing economic burden of chronic liver disease globally, we lack a comprehensive understanding of its financial impact on patients and their families. While there has been an increasing recognition of the financial impact of cancer<sup>5</sup> and cardiovascular disease<sup>6</sup> on patients and their families, we currently lack an understanding of the costs experienced by patients with chronic liver disease and their families across the following domains:

- Financial burden: Patient and family income consumed by healthcare costs<sup>7-9</sup>
- Financial distress: Material, behavioral, and psychological consequences of financial burden<sup>7-11</sup>
- Financial toxicity: Adverse health outcomes of financial distress<sup>5,8,12</sup>

To address this gap, we performed a scoping review of the financial impact of chronic liver disease on patients and families to broadly explore key concepts and available evidence on this topic.<sup>13</sup> Our specific scoping review objectives were to (1) identify the types of financial burden and distress experienced by patients with chronic liver disease and their family caregivers; (2) identify risk factors for financial burden and distress; and (3) describe financial toxicity outcomes in this population. We conclude by proposing a conceptual framework characterizing domains of financial burden, distress and toxicity in chronic liver disease care to guide future research, intervention development, and clinical-, policy-, and system-level changes needed to address current gaps in care.

## **METHODS:**

### **Eligibility Criteria and Study Selection**

To be included in the review, studies needed to examine the prevalence or impact of financial burden and/or distress among patients with chronic liver disease and/or their caregivers. Definitions of financial burden and financial distress were informed by review of the oncology and cardiology literature.<sup>6-8,10,14</sup> Financial burden measures included both direct (healthcare expenditures) and indirect (wage loss) financial burden. Measures of direct financial burden included objective measures such as out-of-pocket healthcare expenditures and subjective measures such as patient- and caregiver-reported difficulty paying medical bills. Measures of indirect financial burden included work loss, absenteeism, and costs of caregiving due to chronic liver disease care. Financial distress measures were classified in three broad domains: (1) material consequences of the costs of chronic liver disease care such as loss of savings, medical debt, and bankruptcy; (2) behavioral coping strategies to manage financial burden including support-seeking and making tradeoffs between medical care and paying for necessities including healthcare; and (3) psychological worry or distress due to financial burden (Figure 1).

Studies were included if they were: (1) peer-reviewed original research; (2) written in English; (3) available in full-text; and (4) involved adult (≥ 18 years old) individuals with chronic liver disease or their caregivers. We included quantitative and mixed-methods studies to examine different methods of assessing financial hardship in this population. Studies were excluded if they did not report patient- or caregiver-level quantitative data on financial burden or distress.

### **Information Sources and Search Strategy**

With the support of one research librarian (LP), we searched the following online databases to identify potentially relevant manuscripts: Ovid MEDLINE, Embase, Cochrane Library, and Web of Science. We limited our search to articles published since the introduction of the Model for End-Stage Liver Disease (MELD) score for liver transplant allocation in February 2002 until July 2021. In addition, we manually examined the citation list of any relevant studies and reviews to identify additional eligible studies. Final searches were conducted between June and July 2021. References were sorted and evaluated for inclusion using the Rayyan application.<sup>15</sup> The search terms and strategy for each database are available in Appendix A.

### **Study Selection and Data Abstraction**

After removal of duplicate citations, two independent reviewers (N.N.U. and N.S.) performed title and abstract screening followed by full-text review to identify potentially eligible studies. Interrater discrepancies for study inclusion were resolved by one additional reviewer (M.S.).

We developed a structured extraction form for study characteristics, including study objective, study design, setting and data source, eligibility criteria, participant demographics and clinical characteristics, definition or measurement of financial burden and distress,

outcome measurements, and key findings. We additionally extracted reported risk factors for financial burden and distress and the association of financial burden and distress variables with patient and caregiver health outcomes (financial toxicity). The extraction form was piloted on a sample of articles and data extraction was completed independently by two reviewers (N.N.U. and N.S.) and reviewed by an additional reviewer (M.S.). All healthcare expenditure data were inflation-adjusted to the year 2021 using the United States Inflation Calculator and Bank of Canada Inflation Calculator and are reported as mean annual expenditures where appropriate.<sup>16,17</sup>

### Conceptual Framework

We integrated the findings from our scoping review with existing models of financial burden in the oncology and cardiology literature to develop a conceptual framework for financial burden, distress, and toxicity in chronic liver disease based on currently-available evidence (Figure 2).<sup>6–11,14</sup>

## RESULTS

### Study Selection

Of 2,336 nonduplicate records screened, with 94 titles, abstracts, and/or full texts reviewed, 19 studies met the final inclusion criteria. The PRISMA flow chart is shown in Figure 3.

### Study and Patient Characteristics

Included studies were conducted between 2007–2021 and patient sample sizes ranged between 96 and 12,998 for a combined sample of 24,549 patients across all the studies. A total of 18 studies used structured surveys and one study used mixed-methods. Most of the studies were from the United States (n=11) followed by Canada (n=3), India (n=3), China (n=1), and Bangladesh (n=1). A few studies focused on patients with a specific etiology of chronic liver disease such as Hepatitis B (HBV) (n=1), Hepatitis C (HCV) (n=2), and alcohol-related liver disease (n=1). Five studies focused on liver transplant recipients (n=5). Three studies included data on caregivers for a total caregiver sample size of 276. Additional study information and patient and caregiver characteristics, including demographic information, are included in Table 1.

### Types of Financial Burden and Distress in Liver Disease

#### Direct Financial Burden

**Catastrophic Financial Burden and Out-of-Pocket Healthcare Expenditures:** A total of seven studies examined direct financial burden in pre- and post-transplant patients with chronic liver disease.<sup>18–24</sup> The prevalence of catastrophic financial burden, defined as annual out-of-pocket healthcare expenditures exceeding 40% of annual household income, ranged between 12%–51% among patients with HBV and other chronic liver diseases in two cross-sectional studies from Bangladesh and China.<sup>18–20</sup> In a 2017 U.S. study by Stepanova et al. conducted using the Medical Expenditure Panel Survey (MEPS), patients with chronic liver disease reported out-of-pocket healthcare expenditures of \$19,390 U.S. dollars (USD) annually (\$22,808 in inflation-adjusted USD) compared to \$5,567 annually (\$6,548 in

inflation-adjusted USD) in patients without liver disease.<sup>4</sup> In a 2021 study by Rakoski et al. using a nationally representative sample of older adults in the U.S., patients with cirrhosis reported paying \$1,075 USD (\$1,306 in inflation-adjusted USD) in annual out-of-pocket healthcare expenditures compared to \$730 USD (\$886 in inflation-adjusted USD) for those without cirrhosis.<sup>21</sup> High out-of-pocket health expenditures were also observed in a 2012 Canadian study by Federico et al. of 738 patients with chronic HCV, in which patients receiving active treatment and those with late-stage disease spent approximately 7% of their annual income on HCV-related healthcare.<sup>22</sup>

Two single-center studies examined financial burden in the post-transplant setting.<sup>23,24</sup> In a 2020 cross-sectional survey study of 96 liver transplant recipients by Peretz et al., patients and families spent a median of \$4,645 Canadian dollars (CAD) (\$4,904 in inflation-adjusted CAD) out-of-pocket during their liver transplant hospitalizations.<sup>23</sup> In a 2017 U.S. study of 333 patients by Rodrigue et al., liver transplant recipients reported spending an average of \$6,480 USD (\$7,368 in inflation-adjusted USD) annually in out-of-pocket for transplant-related medical costs.<sup>24</sup> In this study, 43% of participants reported that health problems related to their transplantation had caused financial problems for themselves or their families.

**Financial Hardship from Medical Bills:** In a 2021 U.S. study by Lago-Hernandez et al. using the National Health Interview Survey (NHIS, 2014–2018), 37% of patients with chronic liver disease reported financial hardship from medical bills, and 14% were unable to pay their medical bills at all.<sup>25</sup> After adjusting for comorbidities, insurance status, and sociodemographic factors, patients with chronic liver disease were significantly more likely to experience hardship from medical bills than adults without chronic liver disease (adjusted OR [aOR] 1.4; 95% confidence interval [CI] 1.27–1.62). In this study, the prevalence of financial hardship from medical bills among patients with chronic liver disease was comparable to diabetes mellitus and chronic kidney disease.

### Indirect Financial Burden

**Worker Productivity Loss:** Rates of unemployment among patients with chronic liver disease ranged from 44%–80% across six observational studies.<sup>4,22,26–29</sup> The 2017 study by Stepanova et al. revealed that the rate of employment among patients with chronic liver disease was substantially lower compared to non-chronic liver disease patients (45% vs. 70%,  $p < 0.0001$ ).<sup>4</sup> In addition, patients with chronic liver disease had significantly lower work productivity due to illness and disability, reporting 3 times more disability days per year compared to controls (10.2 days vs. 3.4 days,  $p < 0.0001$ ).

Two studies reported unemployment rates among liver transplant recipients ranging from 36%–48%.<sup>22,30</sup> In the 2011 study by Federico et al. of 47 HCV transplant recipients, mean annual time costs (time spent seeking healthcare) resulted in the equivalent of 420 hours (over 10 weeks of working time) of lost wages per patient per year.<sup>22</sup> A 2017 study by Beal et al. of 12,998 liver transplant recipients using United Network for Organ Sharing data (2002–2009) revealed that more than 1 in 10 patients had delayed work participation until 3 years or more after their transplant.<sup>30</sup>

**Time and Financial Costs of Informal Caregiving:** Two studies reported out-of-pocket and time costs of informal caregiving for patients with chronic liver disease.<sup>21,22</sup> In a U.S.-based analysis of the Health and Retirement Study (1998–2008) by Rakoski et al., the annual costs of informal caregiving for older individuals with cirrhosis was \$4,700 USD (\$5,707 in inflation-adjusted USD) per person, compared to \$2,100 USD (\$2,550 in inflation-adjusted USD) for age-matched individuals without cirrhosis.<sup>21</sup> In the 2011 Canadian study by Federico et al., time costs of informal caregiving resulted in the equivalent of annual lost wages of \$766 CAD, \$1,050 CAD, and \$2,460 CAD for caregivers of patients with HCV cirrhosis, patients with hepatocellular carcinoma, and liver transplant recipients, respectively.<sup>22</sup>

## Financial Distress

### Material Financial Distress

**Loss of Savings/Assets:** In a 2011 U.S. cross-sectional study by Bajaj et al. of 104 patients with cirrhosis and their caregivers, 54% of families reported that they were unable to add to their personal/family savings and 5% were evicted from their homes due to their medical expenses.<sup>28</sup> In a 2013 multicenter study by Bajaj et al. of 236 patients with cirrhosis, median liquid assets ranged from \$500 - \$4,999 USD (\$598 - \$5,983 in inflation-adjusted USD) in the patient cohort, which reduced to under \$500 USD if current debt was subtracted.<sup>29</sup> In a 2007 study by Rodrigue et al. of 333 adult liver transplant recipients, 57% of patients reported that they needed to use their savings to pay for out-of-pocket medical expenses.

**Medical Debt/Bankruptcy:** Two studies reported a prevalence of medical debt ranging from 24%–46% and medical bankruptcy ranging from 7%–8% of the study populations.<sup>24,28</sup>

### Behavioral Financial Distress

**Support-Seeking:** Five studies reported financial coping behaviors that included support-seeking behaviors such as crowdfunding<sup>28</sup>, increased borrowing<sup>26,31</sup>, pursuing cost-reducing strategies for prescription medications<sup>32</sup>, and family members having to return to work and/or increase their work hours<sup>31</sup> to manage treatment expenses. In one cross-sectional study from India of 132 caregivers of patients with cirrhosis, 25% reported that they had to return to work due to increasing family financial constraints.<sup>31</sup> In the 2011 study by Bajaj et al. of 104 caregivers of patients with cirrhosis, 79% of caregivers reported that they did not have any support for financial advice.<sup>28</sup>

**Tradeoffs for Healthcare:** Multiple studies reported maladaptive coping behaviors in patients with chronic liver disease and their families in response to financial burden from medical care. Three studies examined the impact of financial burden on patient engagement with medical care.<sup>28,32,33</sup> In the 2021 study by Lago-Hernandez et al. of a nationally representative sample of 3,237 patients with chronic liver disease in the U.S., 25% reported experiencing cost-related medication non-adherence.<sup>32</sup> In this analysis, patients with chronic liver disease were significantly more likely to experience cost-related medication non-adherence compared to adults without chronic liver disease (aOR 1.4; 95% CI 1.22–1.61). A 2011 U.S. study of 104 patients by Bajaj et al. revealed that cirrhosis-related medical expenses resulted in 12% of patients missing medical appointments, 12% not taking

medications, 10% taking less medications than prescribed, and 5% missing needed medical procedures.<sup>28</sup> In a 2017 study by Serper et al. of 103 liver transplant recipients from two large U.S. transplant centers, 10% indicated that they could not afford their medications over the past 12 months, and 11% reported that they had to space out their medication frequency due to cost.<sup>33</sup>

**Tradeoffs for Necessities:** Five studies examined the impact of financial burden of chronic liver disease care on patients' abilities to afford necessities such as food and housing.<sup>25,28,32–34</sup> In the study by Lago-Hernandez et al., patients with chronic liver disease experiencing financial burden from medical bills had significantly higher odds of food insecurity (aOR 5.6, 95% CI 3.74–8.37)<sup>25</sup>. In three studies, patients and/or caregivers reported that they had to reduce spending on their children's education in order to afford medical care.<sup>26,28,31</sup>

**Psychological Financial Distress**—Three studies reported the prevalence of psychological financial distress among patients with chronic liver disease ranging from 36% to 63%.<sup>24,25,28</sup> In the 2014–2018 analysis of the NHIS by Lago-Hernandez et al., 36% of U.S. patients with chronic liver disease reported high financial distress regarding their future ability to pay for medical care, housing, and monthly bills, save for retirement, and maintain their standard of living.<sup>25</sup>

### Risks Factors for Financial Burden and Financial Distress

Thirteen out of 19 (68%) manuscripts assessed risk factors associated with experiencing financial burden and financial distress.

Common socioeconomic risk factors were lack of insurance<sup>25,33</sup>, use of public insurance<sup>30,33</sup>, lower income<sup>19,22,25,32,33</sup>, unemployment<sup>24,25,30,33</sup>, lower educational attainment<sup>25,29,30,33</sup>, and lower health literacy<sup>33</sup>. Among liver transplant recipients, individuals who were unemployed in the year preceding their transplant were at increased risk of post-transplant unemployment and financial distress.<sup>30</sup>

Multiple demographic factors were associated with financial hardship and distress. Gender disparity was a common theme, with women at a greater risk of financial burden and distress<sup>25,30,32</sup>. Black patients were found to have higher rates of financial hardship from medical bills<sup>25</sup> and were more likely to report medication trade-offs.<sup>33</sup> Patients who were unmarried were less likely to be employed<sup>4</sup> as were older adults<sup>4,23,28</sup>. Younger age was associated with increased financial hardship from medical bills and cost-related medication non-adherence<sup>25,32</sup>.

Clinical risk factors for financial hardship and distress were examined in multiple studies. Rates of catastrophic financial burden increased with worsening severity of disease (36% compensated cirrhosis, 51% decompensated cirrhosis) in one study of 940 patients with HBV-related disease in China.<sup>19</sup> Other clinical factors associated with an increased risk of financial hardship and/or unemployment included the presence of HCC<sup>3,4</sup>, hepatic encephalopathy<sup>9,14</sup>, and multimorbidity<sup>25,32,33</sup>. In one observational study of liver transplant recipients, an increased risk of post-transplant unemployment was seen among patients who



developed acute rejection (2.17 relative risk ratio [RRR], 95% CI 1.86–2.54) and diabetes mellitus (1.92 RRR, 95% CI 1.67–2.21) after transplantation.<sup>30</sup>

### Financial Toxicity in Liver Disease

Five studies (26%) assessed the association between financial burden, financial distress, and healthcare outcomes. In the 2021 study by Lago-Hernandez et al., patients with chronic liver disease experiencing financial burden from medical bills had significantly higher odds unplanned emergency department visits (aOR 1.85, 95% CI 1.33–2.57).<sup>25</sup> Similarly, financial distress in the form of cost-related medication non-adherence or medication tradeoffs was also associated with unplanned emergency department visits<sup>32</sup> and post-transplant hospital admissions<sup>33</sup> in two U.S.-based studies.

In the 2017 study by Stepanova et al., yearly health expenses were independently associated with a decrease (per every \$10,000 USD) in the Physical Component Scores (beta,  $-0.50 \pm 0.09$ ) and Mental Component Scores (beta,  $-0.25 \pm 0.10$ ) on the Short-Form 12 health-related quality of life survey for patients with chronic liver disease.<sup>4</sup>

In a U.S. cross-sectional study of 73 caregivers of patients with chronic liver disease, loss of income due to caregiving was associated with increased depressive symptoms, anxiety and caregiver burden.<sup>35</sup>

### Conceptual Framework of Financial Burden, Distress, and Toxicity in Chronic Liver Disease

Figure 2 proposes a conceptual framework for domains of financial burden and distress that are associated with financial toxicity outcomes in adult patients with chronic liver disease and their caregivers.

## DISCUSSION

In this scoping review of 19 studies, we found that financial burden and distress are highly prevalent among patients with chronic liver disease and are associated with poor health outcomes for both patients and their caregivers. The prevalence of financial burden and distress in patients with chronic liver disease is comparable to rates observed in patients with other serious illnesses such as chronic kidney disease and type 2 diabetes.<sup>25</sup> Patients with more advanced disease including those with HCC, hepatic encephalopathy, or multimorbidity were at particularly high risk, as were liver transplant recipients. Behavioral financial distress in the form reduced access and adherence to healthcare and other necessities may result in increased pre- and post-transplant healthcare utilization and poor health-related quality of life among patients with chronic liver disease. Unplanned hospital readmissions, uncontrolled illness, and progressive symptomatic disease may in turn be key manifestations of financial toxicity in this population. Despite the high rates of financial toxicity among patients with chronic liver disease, none of the included studies evaluated interventions to alleviate financial burden and distress.

Multiple studies revealed that a diagnosis of chronic liver disease is financially toxic not just for patients but also for their families. The cost of chronic liver disease care resulted in

food insecurity, housing instability, and loss of education, assets and savings for patients and families.<sup>25,26,28,31–34</sup> Caregivers, especially those of patients with hepatic encephalopathy, were particularly affected both in terms of out-of-pocket and time costs of family caregiving as well as changes in their employment and work productivity.<sup>21,22,28,29,31</sup> In many studies, the loss of the patient as the primary breadwinner resulted in substantial financial burden and psychological distress for caregivers, which has been described in prior qualitative studies.<sup>36–39</sup> These findings underscore that interventions addressing financial burden and distress for patients with chronic liver disease must also include a holistic assessment of the needs of their family unit.

Addressing financial burden and identifying financial distress in cirrhosis care will require a multilevel approach (Table 2). At the physician level, increased awareness of and routine screening for financial distress may identify patients with chronic liver disease who are at risk for financial toxicity. Patients who are underinsured, unemployed, have new hepatic encephalopathy or HCC are at particularly high risk for financial burden and may merit early screening and intervention. The question “are you having difficulty paying for your medical care?” is an effective screen for financial distress and additional tools that can be used for screening include the “Costs of Care Conversations” tool from the American College of Physicians and the Comprehensive Score for Financial Toxicity (COST) survey.<sup>40–43</sup> Clinicians providing care to liver transplant recipients of working age should assess whether they have returned to work and screen for work absenteeism. Additionally, during routine medication reconciliation in outpatient visits, clinicians should discuss low-cost alternatives with patients. At the clinic and hospital level, new models of care using social workers, community health workers, pharmacists and/or financial navigators to help patients and their families navigate employment benefits and family leave, access assistance for prescriptions, unemployment and nonmedical costs, and obtain financial counseling are needed.<sup>44,45</sup> There should be an increasing recognition of the non-medical costs of care such as time and transportation, with consideration of telehealth visits, parking vouchers, or hospital at home models of care to alleviate these burdens on patients and their caregivers.<sup>46–50</sup> Additionally, addressing cost-related barriers to care may require the development of clinic-based strategies and clinical guidelines to increase cost transparency, guide shared decision-making around cost-benefit tradeoffs, and improve delivery of high-value hepatology care.<sup>51</sup> At a policy and system level, promoting legislation for insurance coverage of high-cost medications such as immunosuppressive drugs, value-based drug-pricing, assistance programs for caregivers, and paid family and medical leave are needed.<sup>52–55</sup>

More research on the financial impact of chronic liver disease on patients and caregivers is needed in four key areas. First, the current body of evidence on financial burden, distress and toxicity in chronic liver disease is predominantly from small-sample observational studies with limited outcomes assessments which are prone to biases. There is a need for large, well-typified prospective longitudinal studies assessing different domains of financial burden and distress and causal mechanisms from the time of diagnosis of chronic liver disease to the development of relevant financial and healthcare outcomes to identify risk factors. Second, methods and measures for financial burden and distress varied widely, limiting comparisons across studies. Notably, no study used a standardized instrument such as the Comprehensive Score for Financial Toxicity survey that has been validated in the oncology population.<sup>41,56</sup>

Third, the included studies provided limited data on race/ethnicity, insurance status, care setting (e.g. rural, urban), or other social determinants of health of the patient and/or caregiver participants. Financial burden represents just one social determinant of health that is impacted by many upstream factors, including systemic policies, socioeconomic status, insurance access, racism, and bias.<sup>57</sup> Future research in this area should proactively recruit diverse populations with formal tracking of social determinants of health and should assess for pharmaco-equity in cirrhosis care, in which all individuals, regardless of background, have access to evidence-based medications and treatments.<sup>58,59</sup> Fourth, as the population of patients with chronic liver disease aged 65 years or older continues to increase, assessing risk factors for financial burden among the Medicare eligible population and outcomes related to costs of care at end-of-life will be an important area for future study.<sup>60–62</sup> Lastly, future research is needed to develop and test evidence-based interventions targeting different domains of financial burden and distress.

### Conclusions

Observational evidence supports the findings that financial burden and distress are highly prevalent among patients with chronic liver disease and their caregivers and are associated with poor health outcomes. Despite these findings, there is a substantial evidence gap on the measurement of patient-level financial burden and distress, causal mechanisms, and outcomes. There is a critical need for patient- and caregiver-centered interventions to alleviate financial burden and distress and reduce financial toxicity in chronic liver disease care.

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### Appendix

### Appendix

### Database:

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

#	Query
1	liver diseases/ or exp Hepatic Insufficiency/ or exp Liver Cirrhosis/ or exp Liver Transplantation/ or exp Liver Neoplasms/ or exp fatty liver/
2	("Liver Disease" or "liver diseases" or "liver failure" or "liver fibrosis" or cirrhosis or "liver transplant" or "liver transplants" or "liver transplantation" or "liver cell cancer" or "liver cell cancers" or "liver cancer" or "liver cancers" or cirrhosis or "hepatocellular carcinoma" or HCC or hepatoma or hepatomas or "hepatic encephalopathy" or "hepatic insufficiency" or "fatty liver").ti,ab.
3	1 or 2

#	Query
4	exp "Cost of Illness"/ or exp Health Care Costs/ or exp Health Expenditures/ or exp financing personal/
5	(financial adj4 burden).ti,ab.
6	((cost or costs) adj2 (treatment or care or illness or healthcare or "health care" or direct)).ti,ab.
7	("Financial security" or "Financial status" or "Financial toxicity" or "Financial stress" or "Financial strain" or "Financial hardship*" or "Financial distress" or "Financial difficult*" or "Financial concern*" or "financial consequences" or "Financial costs" or Finances or "Out of pocket" or Copay* or "co pay*" or "cost sharing" or Bankruptcy or "medical debt" or "medical expenses" or "medical expenditures" or "health care expenditure*" or "healthcare expenditure*" or "Socioeconomic status" or "economic status" or "economic consequences" or "Socioeconomic burden" or "economic hardship*" or "economic burden").ti,ab.
8	(Patient* or Caregiver* or carers or Family or families or Personal or individual or individuals).ti,ab.
9	exp "Patients"/ or exp "Caregivers"/ or exp "Family"/
10	5 or 6 or 7
11	8 or 9
12	10 and 11
13	4 or 12
14	3 and 13

**Database:**

[Embase.com](https://www.embase.com) (via Elsevier)

#	Query
1	'chronic liver disease'/exp OR 'liver failure'/de OR 'liver cirrhosis'/exp OR 'liver cancer'/exp OR 'fatty liver'/exp OR 'liver fibrosis'/de OR 'liver transplantation'/exp OR 'hepatic encephalopathy'/exp
2	'liver disease':ab,ti OR 'liver diseases':ab,ti OR 'liver failure':ab,ti OR 'liver fibrosis':ab,ti OR 'liver transplant':ab,ti OR 'liver transplants':ab,ti OR 'liver transplantation':ab,ti OR 'liver cell cancer':ab,ti OR 'liver cell cancers':ab,ti OR 'liver cancer':ab,ti OR 'liver cancers':ab,ti OR cirrhosis:ab,ti OR 'hepatocellular carcinoma':ab,ti OR hcc:ab,ti OR hepatoma:ab,ti OR hepatomas:ab,ti OR 'hepatic encephalopathy':ab,ti OR 'hepatic insufficiency':ab,ti OR 'fatty liver':ab,ti
3	#1 OR #2
4	'financial burden'/de OR 'financial stress'/exp OR 'out of pocket cost'/de OR 'out of pocket expenditure'/de OR 'financial management'/de OR 'economic burden'/de OR 'cost of illness'/de OR 'health care cost'/exp OR 'personal finance'/exp
5	(financial NEAR/4 burden):ab,ti
6	((cost OR costs) NEAR/2 (treatment OR care OR illness OR healthcare OR 'health care' OR direct)):ab,ti
7	'financial security':ab,ti OR 'financial status':ab,ti OR 'financial toxicity':ab,ti OR 'financial stress':ab,ti OR 'financial strain':ab,ti OR 'financial hardship*':ab,ti OR 'financial distress':ab,ti OR 'financial difficult*':ab,ti OR 'financial concern*':ab,ti OR 'financial consequences':ab,ti OR 'financial costs':ab,ti OR finances:ab,ti OR 'out of pocket':ab,ti OR copay*:ab,ti OR 'co pay*':ab,ti OR 'cost sharing':ab,ti OR bankruptcy:ab,ti OR 'medical debt':ab,ti OR 'medical expenses':ab,ti OR 'medical expenditures':ab,ti OR 'health care expenditure*':ab,ti OR 'healthcare expenditure*':ab,ti OR 'socioeconomic status':ab,ti OR 'economic status':ab,ti OR 'economic consequences':ab,ti OR 'socioeconomic burden':ab,ti OR 'economic hardship*':ab,ti OR 'economic burden':ab,ti
8	patient*:ab,ti OR caregiver*:ab,ti OR carers:ab,ti OR family:ab,ti OR families:ab,ti OR personal:ab,ti OR individual:ab,ti OR individuals:ab,ti
9	'patient'/exp OR 'caregiver'/de OR 'family'/de
10	#4 OR #5 OR #6 OR #7
11	#8 OR #9

#	Query
12	#3 AND #10 AND #11
13	#3 AND #10 AND #11 AND ([medline]/lim OR [pubmed-not-medline]/lim)
14	#13 NOT #13

**Database:**

Cochrane Library via Ovid

#	Query
1	liver diseases/ or exp Hepatic Insufficiency/ or exp Liver Cirrhosis/ or exp Liver Transplantation/ or exp Liver Neoplasms/ or exp fatty liver/
2	("Liver Disease" or "liver diseases" or "liver failure" or "liver fibrosis" or cirrhosis or "liver transplant" or "liver transplants" or "liver transplantation" or "liver cell cancer" or "liver cell cancers" or "liver cancer" or "liver cancers" or cirrhosis or "hepatocellular carcinoma" or HCC or hepatoma or hepatomas or "hepatic encephalopathy" or "hepatic insufficiency" or "fatty liver").ti,ab.
3	1 or 2
4	exp "Cost of Illness"/ or exp Health Care Costs/ or exp Health Expenditures/ or exp financing personal/
5	(financial adj4 burden).ti,ab.
6	((cost or costs) adj2 (treatment or care or illness or healthcare or "health care" or direct)).ti,ab.
7	("Financial security" or "Financial status" or "Financial toxicity" or "Financial stress" or "Financial strain" or "Financial hardship*" or "Financial distress" or "Financial difficult*" or "Financial concern*" or "financial consequences" or "Financial costs" or Finances or "Out of pocket" or Copay* or "co pay*" or "cost sharing" or Bankruptcy or "medical debt" or "medical expenses" or "medical expenditures" or "health care expenditure*" or "healthcare expenditure*" or "Socioeconomic status" or "economic status" or "economic consequences" or "Socioeconomic burden" or "economic hardship*" or "economic burden").ti,ab.
8	(Patient* or Caregiver* or carers or Family or families or Personal or individual or individuals).ti,ab.
9	exp "Patients"/ or exp "Caregivers"/ or exp "Family"/
10	5 or 6 or 7
11	8 or 9
12	10 and 11
13	4 or 12
14	3 and 13
15	Remove duplicates from 14

**Database:**

Web of Science Core Collection via Clarivate

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#	Query
1	TOPIC: ((“Liver Disease” or “liver diseases” or “liver failure” or “liver fibrosis” or cirrhosis or “liver transplant” or “liver transplants” or “liver transplantation” or “liver cell cancer” or “liver cell cancers” or “liver cancer” or “liver cancers” or cirrhosis or “hepatocellular carcinoma” or HCC or hepatoma or hepatomas or “hepatic encephalopathy” or “hepatic insufficiency” or “fatty liver”))
2	TOPIC: (financial NEAR/4 burden)
3	TOPIC: ((cost or costs) NEAR/2 (treatment or care or illness or healthcare or “health care” or direct))
4	TOPIC: ((“Financial security” or “Financial status” or “Financial toxicity” or “Financial stress” or “Financial strain” or “Financial hardship*” or “Financial distress” or “Financial difficult*” or “Financial concern*” or “financial consequences” or “Financial costs” or Finances or “Out of pocket” or Copay* or “co pay*” or “cost sharing” or Bankruptcy or “medical debt” or “medical expenses” or “medical expenditures” or “health care expenditure*” or “healthcare expenditure*” or “Socioeconomic status” or “economic status” or “economic consequences” or “Socioeconomic burden” or “economic hardship*” or “economic burden”))
5	TOPIC: ((Patient* or Caregiver* or carers or Family or families or Personal or individual or individuals))
6	#2 OR #3 OR #4
7	#6 AND #5 AND #1

## Abbreviations:

<b>CAD</b>	Canadian Dollars
<b>HBV</b>	Hepatitis B Virus
<b>HCV</b>	Hepatitis C Virus
<b>HCC</b>	Hepatocellular Carcinoma
<b>MEPS</b>	Medical Expenditure Panel Survey
<b>MELD</b>	Model for End-Stage Liver Disease
<b>NHANES</b>	National Health and Nutrition Examination Survey
<b>NHIS</b>	National Health Interview Survey
<b>UNOS</b>	United Network for Organ Sharing
<b>USD</b>	United States Dollars

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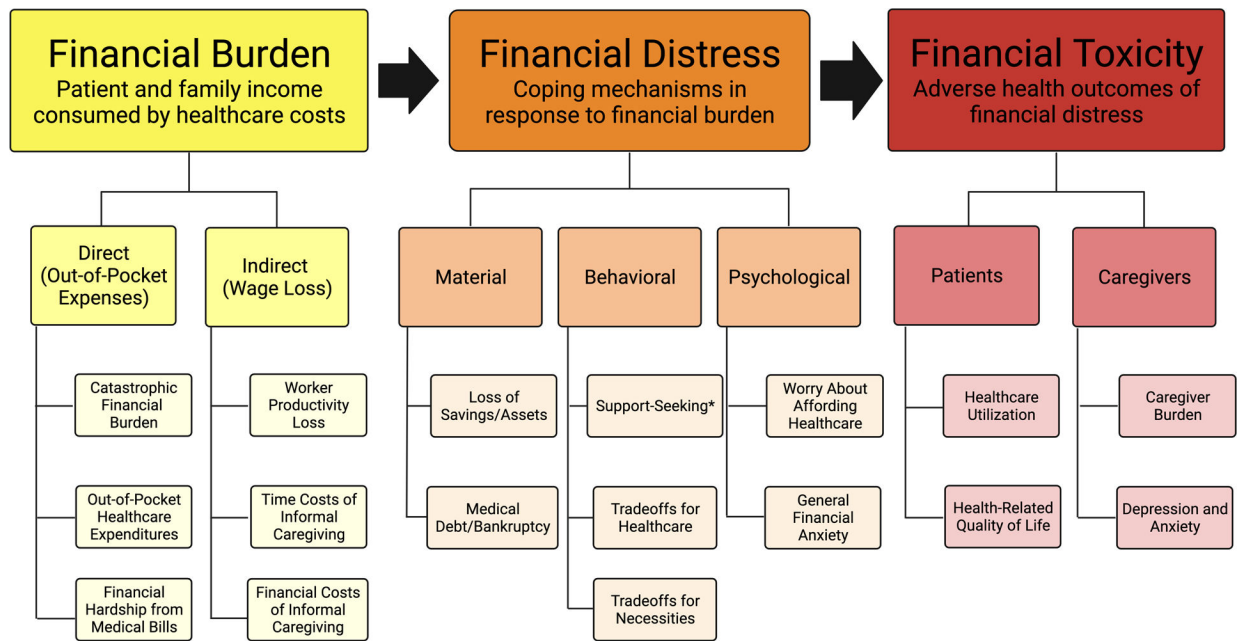


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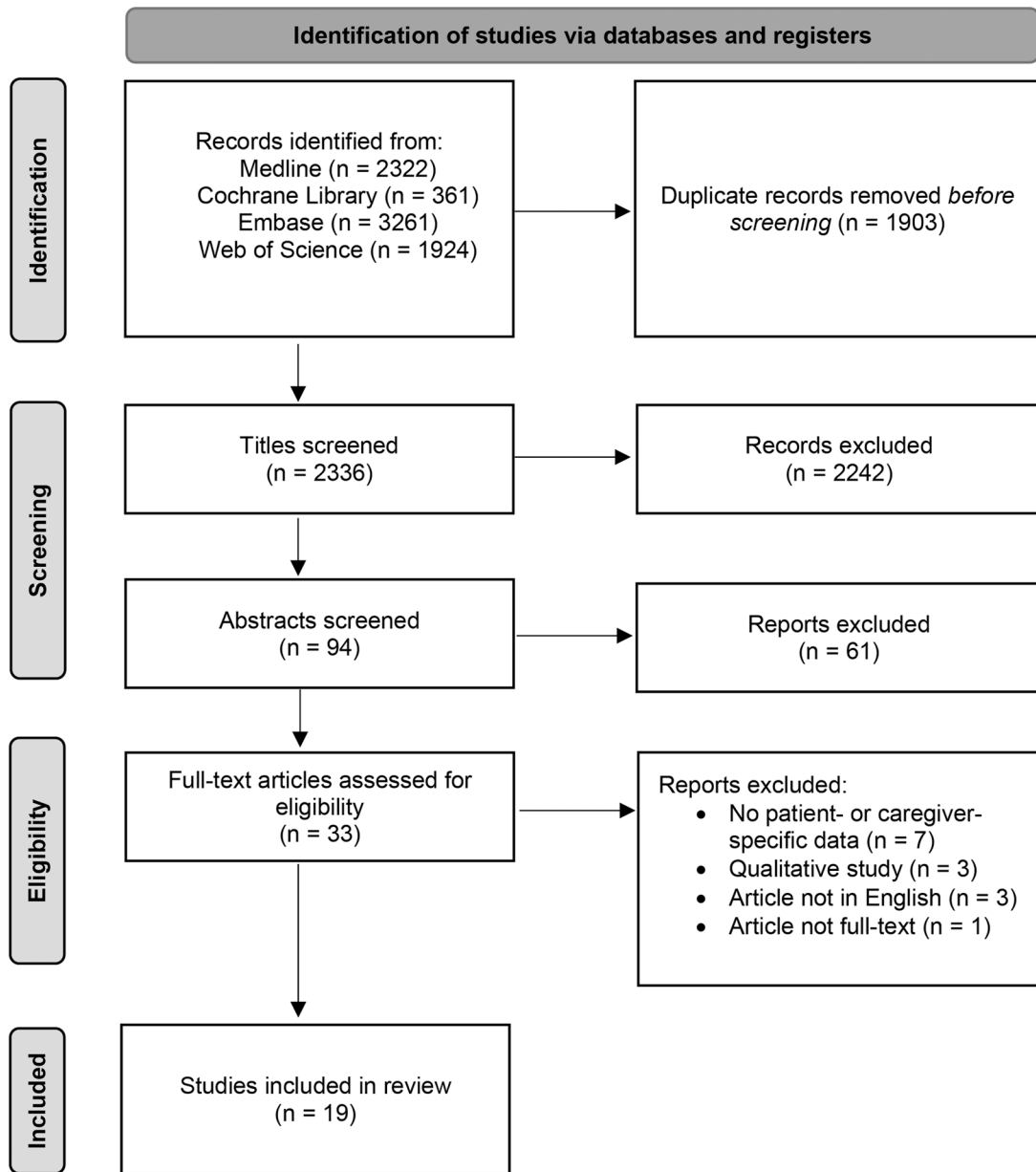
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**Figure 1:** Domains of Financial Burden and Distress in Chronic Liver Disease Care.



**Figure 2:**  
**Conceptual Framework of Financial Burden, Financial Distress, and Financial Toxicity in Chronic Liver Disease Care.** \*Support-seeking includes financial coping behaviors such as crowdfunding, increased borrowing, pursuit of cost-reducing strategies for medical care, and caregivers increasing their work capacity.



**Figure 3:**  
Flow Diagram of Study Selection

Table 1.

Characteristics of Included Studies

Reference	Study Description	Study Design Setting/Data Source (Subjects, n)	Study Inclusion Criteria Participant Demographics	Financial Burden and Financial Distress Measures: Definition, Prevalence	Financial Toxicity Outcomes
Lago-Hernandez et al., 2021 (USA) <sup>32</sup>	To estimate the prevalence, risk factors, and consequences of cost-related medication non-adherence in individuals with chronic liver disease	Cross-sectional NHIS, 2014–2018 (n=3,237)	<p>Patients with chronic liver disease</p> <ul style="list-style-type: none"> <li>• 27% aged 65 y, 57% 40–64 y, 16% 18–39 y</li> <li>• 48% men</li> <li>• 67% non-Hispanic white, 18% Hispanic, 7% Black, 5% Asian</li> <li>• 7% uninsured</li> </ul>	<p><b>Behavioral Financial Distress (Tradeoffs for Healthcare):</b> Cost-related medication nonadherence</p> <ol style="list-style-type: none"> <li><b>1</b> Needed but could not afford medications</li> <li><b>2</b> Delayed filling prescriptions</li> <li><b>3</b> Took less medication to save</li> <li><b>4</b> Skipped medication doses to save</li> </ol> <p><b>Prevalence:</b> 25% reported cost-related medication nonadherence</p> <ul style="list-style-type: none"> <li>• Patients with chronic liver disease more likely to experience cost-related medication nonadherence than adults without chronic liver disease (aOR 1.40; 95% CI 1.22–1.61)</li> </ul>	<p>Among chronic liver disease patients, cost-related medication nonadherence was associated with:</p> <ul style="list-style-type: none"> <li>• 5.1x higher odds of financial hardship from medical bills (aOR 5.05, 95% CI 3.73–6.83)</li> <li>• 4.3x higher odds of financial distress (aOR 4.28, 95% CI 3.19–5.76)</li> <li>• 9.3x higher odds of engaging in cost-reducing behaviors (aOR 9.3, 95% CI 6.9–12.7)</li> <li>• 2.9x higher odds of food insecurity (aOR 2.85, 95% CI 2.02–4.01)</li> <li>• 1.5x higher odds of emergency department visits (aOR 1.46, 95% CI 1.11–1.94)</li> <li>• 1.6x higher odds of health-related work absenteeism (aOR 1.62, 95% CI 1.2–2.19)</li> </ul>
Lago-Hernandez et al., 2021 (USA) <sup>25</sup>	To estimate the national burden and consequences of financial hardship from medical bills	Cross-sectional NHIS, 2014–2018 (n=3,666)	<p>Patients with chronic liver disease</p> <ul style="list-style-type: none"> <li>• 25% aged 65 y, 56% 40–64 y, 19% 18–39 y</li> <li>• 50% male</li> </ul>	<p><b>Direct Financial Burden (Financial Hardship from Medical Bills):</b></p> <ol style="list-style-type: none"> <li><b>1</b> Having problems paying medical bills in the past 12 months</li> </ol>	<p>Among chronic liver disease patients, being unable to pay medical bills was associated with:</p> <ul style="list-style-type: none"> <li>• 8.4x higher odds of cost-related</li> </ul>

Reference	Study Description	Study Design Setting/Data Source (Subjects, n)	Study Inclusion Criteria Participant Demographics	Financial Burden and Financial Distress Measures: Definition, Prevalence	Financial Toxicity Outcomes
Peretz et al., 2020 (Canada) <sup>23</sup>	To document the psychological and financial impact of having to travel long distances for liver transplantation in adult liver disease patients	Cross-sectional Health Sciences Center, Winnipeg, Manitoba, Canada; 2018–2019 (n=96)	<ul style="list-style-type: none"> <li>65% non-Hispanic white, 19% Hispanic, 8% Black, 5% Asian</li> <li>8% uninsured</li> </ul>	<p>2 Currently having medical bills being paid off over time</p> <p>3 Unable to pay medical bills at all</p> <p><b>Psychological Financial Distress (Worry about Affording Healthcare):</b></p> <p>1 Ability to pay medical costs of illness/accident, usual health care, rent/mortgage/housing costs, or monthly bills</p> <p>2 Save for retirement</p> <p>3 Maintain standard of living</p> <p><b>Prevalence:</b></p> <ul style="list-style-type: none"> <li>37% of patient reported financial hardship from medical bills</li> <li>14% of patient were unable to pay medical bills at all</li> <li>36% reported high financial distress</li> <li>Patients with chronic liver disease more likely to experience hardship from medical bills than adults without chronic liver disease (aOR, 1.43; 95% CI, 1.27–1.62)</li> <li>Prevalence of financial hardship from medical bills for patients with chronic liver disease comparable to that observed among patients with Type 2 diabetes (aOR, 0.9; 95% CI, 0.8–1.1) and chronic kidney disease (aOR, 1.1; 95% CI, 0.9–1.3) but lower than that observed among patients with cardiovascular disease (aOR, 1.4; 95% CI, 1.1–1.9)</li> </ul>	<ul style="list-style-type: none"> <li>medication nonadherence (aOR 8.39, 95% CI 5.72–12.32)</li> <li>6.3x higher odds of financial distress (aOR 6.33, 95% CI 4.44–9.03)</li> <li>5.6x higher odds of food insecurity (aOR 5.59, 95% CI 3.74–8.37)</li> <li>1.9x higher odds of emergency department visits (aOR 1.85, 95% CI 1.33–2.57)</li> <li>1.8x higher odds of health-related work absenteeism (aOR 1.83, 95% CI 1.26–2.67)</li> </ul>
			<p>Liver transplant recipients</p> <ul style="list-style-type: none"> <li>Mean age at transplant of 43 y (34% &gt; 60 y)</li> <li>59% male</li> <li>18% HCV, 11% PSC, 10% AIH, 9% ALLD,</li> </ul>	<p><b>Direct Financial Burden (Out-of-Pocket Healthcare Expenditures)</b> for patients and/or their families/friends during the liver transplant hospitalization:</p> <ul style="list-style-type: none"> <li>Median out-of-pocket expenses was \$4,645 CAD (range \$0-\$17,624) to cover needs such as transportation, accommodations, and food</li> </ul>	N/A

Reference	Study Description	Study Design Setting/Data Source (Subjects, n)	Study Inclusion Criteria Participant Demographics	Financial Burden and Financial Distress Measures: Definition, Prevalence	Financial Toxicity Outcomes
Pol et al., 2019 (Canada) <sup>34</sup>	To increase understanding of the motivations and outcomes of organ transplantation crowdfunding	Mixed-methods Canadian adult liver transplantation campaigns posted to GoFundMe; May 2018 (n=134)	Adult liver transplant candidates  7% PBC, 6% NAEFL, 38% unknown	<b>Behavioral Financial Distress (Support-Seeking):</b> Crowdfunding  <ul style="list-style-type: none"> <li>On average liver campaigns received \$8,346.77 CAD</li> <li>The majority of campaigns (78%) characterized liver transplantation as a financial burden, with the most common reasons for requesting funding as follows: caregiver expenses (38%), patient relocation expenses (34%), patient living expenses (32%)</li> </ul>	N/A
Lu et al., 2019 (USA) <sup>65</sup>	To examine hepatitis C virus (HCV) medication use and costs in a commercially insured population	Retrospective Harvard Pilgrim Health Care medical and pharmacy claims data, 2012–2015 (n=3,091)	Patients with chronic HCV infection  <ul style="list-style-type: none"> <li>8% aged 65 y, 62% 50–64 y, 20% 30–49 y, 10% 18–29 y</li> <li>66% male</li> <li>78% White, 20% Black mixed race, 2% Black</li> </ul>	<b>Direct Financial Burden (Out-of-Pocket Healthcare Expenditures)</b> on HCV medications  <ul style="list-style-type: none"> <li>Following availability of new direct-acting antivirals, average yearly out-of-pocket spending on HCV medications increased from \$41 USD to \$94 USD per HCV-diagnosed member in the study population, with about 32% of members receiving HCV medications.</li> <li>In adjusted pre–post analyses, the absolute change was \$53 USD (95% CI, \$9 USD - \$97 USD) per member per year and the relative change was 131% (95% CI, 15%–247%)</li> </ul>	N/A
Beal et al., 2017 (USA) <sup>30</sup>	To examine patterns of employment discontinuity among liver transplant recipients and evaluate clinical, demographic, and economic factors that may contribute to delayed or unstable employment	Retrospective UNOS, 2002–2009 (n=12,998)	Deceased donor liver transplant recipients at least 5 years post-transplant  <ul style="list-style-type: none"> <li>Mean age at transplant 49 y</li> <li>71% male</li> <li>75% White, 9% Black, 16% Other</li> <li>26% HCV, 10% cholestatic liver disease, 19% alcohol, 15% HCC, 30% other</li> </ul>	<b>Indirect Financial Burden (Worker Productivity Loss):</b> Patient employment status after liver transplantation  <ul style="list-style-type: none"> <li>36% of patients were never employed post-transplant</li> <li>29% of patients returned to work within 2 years of transplant and remained employed</li> <li>23% of patients returned to work within 2 years of transplant but subsequently became unemployed</li> </ul>	N/A



Reference	Study Description	Study Design Setting/Data Source (Subjects, n)	Study Inclusion Criteria Participant Demographics	Financial Burden and Financial Distress Measures: Definition, Prevalence	Financial Toxicity Outcomes
Singh et al., 2016 (India) <sup>26</sup>	To estimate the socioeconomic impact of alcohol use on patients with alcohol-related liver disease and their families	Cross-sectional Shrirama Chandra Bhanj Medical College and Hospital, Cuttack, Odisha, India, 2013–2014 (n=100)	Patients with alcohol-related liver disease <ul style="list-style-type: none"> <li>• 37% &gt; 50 y, 60% 30–50y, 3% &lt; 30 y</li> <li>• 100% male</li> </ul>	<ul style="list-style-type: none"> <li>• 12% of patients returned to work 3 years post-transplant</li> </ul> <p><b>Indirect Financial Burden (Worker Productivity Loss):</b></p> <ul style="list-style-type: none"> <li>• 80% were absent from their work due to alcohol-related problems with average duration of work absenteeism of 12 weeks</li> </ul> <p><b>Behavioral Financial Distress (Support-Seeking):</b> Increased borrowing</p> <ul style="list-style-type: none"> <li>• 86% of patients borrowed money from friends/relatives for treatment expenses</li> </ul> <p><b>Behavioral Financial Distress (Tradeoffs for Necessities):</b> Tradeoffs for education</p> <ul style="list-style-type: none"> <li>• For 43% of patients, their children were deprived of education due to financial burden</li> </ul>	N/A
Stepanova et al., 2017 (USA) <sup>4</sup>	To assess the effects of chronic liver disease on quality of life and work productivity as well as its economic burden in the US	Cross-sectional MEPS, 2004–2013 and NHANES (1999–2012) (n=1,864)	Patients with chronic liver disease <ul style="list-style-type: none"> <li>• Mean age 54 y</li> <li>• 49% male</li> <li>• 70% non-Hispanic White, 10% Black, 13% Hispanic, 4% Asian</li> <li>• 9% uninsured</li> </ul>	<p><b>Direct Financial Burden (Out-of-Pocket Healthcare Expenditures):</b></p> <ul style="list-style-type: none"> <li>• Patients with chronic liver disease had annual healthcare expenses of \$19,390 USD compared to \$5,567 for adults without chronic liver disease</li> </ul> <p><b>Indirect Financial Burden (Worker Productivity Loss):</b></p> <ul style="list-style-type: none"> <li>• 45% of chronic liver disease patients were employed (compared with 70% without liver disease, p &lt; 0.0001)</li> <li>• Patients with chronic liver disease were more likely to not work due to their illness or disability (31% vs. 7%) and had 3 times more disability days per year (10.2 days vs. 3.4 days)</li> <li>• The presence of chronic liver disease was independent predictor of employment (OR 0.6, 95% CI 0.5–0.71)</li> </ul>	Yearly health expenses (per \$10,000 USD) were independently associated with a decrease in the Physical Component Score (Beta = -0.5 ± 0.09) and Mental Component Score (-0.25 ± 0.10) of the Short-Form 12 health-related quality of life survey

Reference	Study Description	Study Design Setting/Data Source (Subjects, n)	Study Inclusion Criteria Participant Demographics	Financial Burden and Financial Distress Measures: Definition, Prevalence	Financial Toxicity Outcomes
Che et al., 2016 (China) <sup>19</sup>	To investigate the financial burden of various stages of hepatitis B (HBV)-related diseases and the level of alleviation from financial burden by health insurance schemes in Yunnan province of China	Cross-sectional First Affiliated Hospital of Kunming Medical University, 2012–2013 (n=940)	Patients with chronic HBV, compensated HBV cirrhosis, decompensated HBV cirrhosis, and HBV with HCC <ul style="list-style-type: none"> <li>• Mean age 44 y</li> <li>• 66% male</li> <li>• 55% HBV, 10% compensated, 21% decompensated, 14% HCC</li> </ul>	<b>Direct Financial Burden (Catastrophic Financial Burden):</b> Household's out-of-pocket expenses exceeding 40% of household's capacity to pay <ul style="list-style-type: none"> <li>• 36% compensated, 51% decompensated, 50% HCC patients had catastrophic health expenditures after health insurance reimbursement</li> </ul>	N/A
Rakoski et al., 2012 (USA) <sup>21</sup>	To assess health status and functional disability of older individuals with cirrhosis and its complications, as well as estimate the burden and cost of informal caregiving in this population	Prospective longitudinal Health and Retirement survey linked to Center for Medicare and Medicaid Services, 1998–2008 (n=371)	Patients > 50y with cirrhosis <ul style="list-style-type: none"> <li>• Mean age 75 y</li> <li>• 45% male</li> <li>• 72% White, 14% Black, 13% Hispanic</li> </ul>	<b>Direct Financial Burden (Out-of-Pocket Healthcare Expenditures):</b> Self-reported over the previous two years <ul style="list-style-type: none"> <li>• Median \$2,150 USD (\$526–\$5,379) for patients with cirrhosis versus \$1,459 USD (\$433–\$3,709) for those without cirrhosis, p&lt;0.001</li> </ul> <b>Indirect Financial Burden (Financial Costs of Informal Caregiving)</b> <ul style="list-style-type: none"> <li>• Annual cost of informal caregiving for elderly individuals with cirrhosis was \$4,700 USD per person (compared to \$2,100 USD for age matched elderly individuals without cirrhosis)</li> </ul>	N/A
Hareendran et al., 2020 (India) <sup>31</sup>	To study the quality of life, psychosocial burden and prevalence of mental health disorders among caregivers	Cross-sectional Government Medical College Trivandrum, South India, 2018–2019 (n=132)	Primary caregivers of patients with cirrhosis <ul style="list-style-type: none"> <li>• Mean caregiver age of 41</li> <li>• 11% male</li> </ul>	<b>Behavioral Financial Distress (Support-Seeking):</b> <ul style="list-style-type: none"> <li>• 25% of caregivers were forced to work due to financial constraints</li> <li>• 20% of families had to take a loan to pay for medical expenses</li> </ul> <b>Behavioral Financial Distress (Tradeoffs for Necessities):</b> <ul style="list-style-type: none"> <li>• 9% of families had their children's education be hampered due to financial constraints</li> </ul>	Increased cost of cirrhosis treatment was associated with an increased risk of depression and anxiety among caregivers
Rodrigue et al., 2007 (USA) <sup>24</sup>	To survey liver transplant and kidney transplant recipients about the financial impact	Cross-sectional University of Florida, 1995–2004 (n=333)	Liver transplant recipients <ul style="list-style-type: none"> <li>• Mean age 57 y</li> <li>• 69% male</li> </ul>	<b>Direct Financial Burden (Out-of-Pocket Healthcare Expenditures):</b> Estimated monthly out-of-pocket expenses	N/A

Reference	Study Description	Study Design Setting/Data Source (Subjects, n)	Study Inclusion Criteria Participant Demographics	Financial Burden and Financial Distress Measures: Definition, Prevalence	Financial Toxicity Outcomes
	of transplantation and to ascertain the strategies they used to manage non-reimbursed expenses related to transplantation		<ul style="list-style-type: none"> <li>81% White</li> </ul>	<ul style="list-style-type: none"> <li>Liver transplant recipients reported spending \$540 USD/month on medical expenses</li> </ul> <p><b>Material Financial Distress (Loss of Savings/Assets, Medical Debt/Bankruptcy):</b> To pay for out-of-pocket health expenses, patients reported the following:</p> <ul style="list-style-type: none"> <li>57% used personal/family savings</li> <li>24% used credit cards</li> <li>8% declared bankruptcy</li> </ul>	
Shrestha et al., 2019 (India) <sup>27</sup>	To evaluate the burden on the informal caregivers of patients with cirrhosis and the factors responsible for this burden in a population in Northern India	Cross-sectional Post-graduate institute of Medical Education and Research, Northern India, 2015 (n=200; 100 patients and 100 caregivers)	<p>Patients with cirrhosis and their informal caregivers</p> <ul style="list-style-type: none"> <li>Caregivers mean age 47</li> <li>66% female</li> </ul>	<p><b>Indirect Financial Burden (Worker Productivity Loss):</b></p> <ul style="list-style-type: none"> <li>44% of patients in the study were currently employed</li> </ul>	N/A
Rahman et al., 2020 (Bangladesh) <sup>18</sup>	To estimate the cost of illnesses among a population in urban Bangladesh and to assess the household financial burden associated with these diseases	Cross-sectional Rajshahi, Bangladesh, 2011 (n=41)	Household members with self-reported liver disease	<p><b>Direct Financial Burden (Catastrophic Financial Burden):</b> Household's out-of-pocket expenses exceeding 40% of household's capacity to pay</p> <ul style="list-style-type: none"> <li>Incidence of catastrophic healthcare expenditure was 12.3% among individuals with liver disease</li> </ul>	N/A
Federico et al., 2012 (Canada) <sup>22</sup>	To evaluate time costs (time spent seeking healthcare) and out-of-pocket costs for patients with hepatitis C (HCV) and their caregivers	Cross-sectional University of British Columbia, 2006–2008 (n=738)	<p>Patients with HCV</p> <ul style="list-style-type: none"> <li>Chronic HCV infection (n=326), cirrhosis (n=135), HCC (n=21), transplant recipients (n=47)</li> <li>Mean age 54 y</li> <li>60% male</li> <li>86% White</li> </ul>	<p><b>Direct Financial Burden (Out-of-Pocket Healthcare Expenditures):</b></p> <ul style="list-style-type: none"> <li>Patients receiving active treatment and those with late-stage disease spent over \$2000 CAD per year on HCV-related healthcare, which represented approximately 7% of their annual income.</li> </ul> <p><b>Indirect Financial Burden (Time Costs of Informal Caregiving):</b> Patient and caregiver time costs (calculated time spent seeking healthcare by hourly value determined by patient/caregiver reported income and/or age- and gender-stratified wage rates). All time was valued as hours/weeks of employment</p>	N/A

Reference	Study Description	Study Design Setting/Data Source (Subjects, n)	Study Inclusion Criteria Participant Demographics	Financial Burden and Financial Distress Measures: Definition, Prevalence	Financial Toxicity Outcomes
Bajaj et al., 2013 (USA) <sup>29</sup>	To investigate the socioeconomic status and cognition in a multicenter study of cirrhosis	Cross-sectional Multicenter (Virginia Commonwealth University, University of Rome, Case Western University), 2012 (n=236)	<p>Patients with cirrhosis</p> <ul style="list-style-type: none"> <li>14% had prior history of overt hepatic encephalopathy</li> <li>Mean age 58y</li> </ul>	<ul style="list-style-type: none"> <li>The average annual time loss attributable to HCV and its treatment varied from 69 hours in early disease to 426 hours among transplant recipients.</li> <li>For transplant recipients, this represented over 10 weeks of working time, or 20% of the average number of working hours among employed Canadians annually.</li> <li>Caregivers of transplant recipients had an average of 3 weeks of annual time loss due to caregiving</li> </ul> <p><b>Indirect Financial Burden (Worker Productivity Loss):</b></p> <ul style="list-style-type: none"> <li>48% of patients were unemployed</li> </ul>	N/A
Bajaj et al., 2011 (USA) <sup>28</sup>	To study the emotional and socioeconomic burden of cirrhosis and hepatic encephalopathy on patients and informal caregivers	Cross-sectional Virginia Commonwealth University, 2009–2010 (n=104)	<p>Patients with cirrhosis and their informal caregivers</p> <ul style="list-style-type: none"> <li>Mean age 58 y</li> <li>70% male</li> <li>83% White, 12% Black, 5% Hispanic</li> <li>44% HCV, 23% NASH, 11% EtOH + HCV, 7% EtOH, 15% others</li> </ul>	<p><b>Material Financial Distress (Loss of Savings/ Assets, Medical Debt/Bankruptcy):</b></p> <ul style="list-style-type: none"> <li>If patients lost all sources of income, they could maintain their current standard of living for 3–6 months. After liquidation of all resources, the median finances available would be reduced to \$500 USD – \$4,999 USD if current debt was subtracted</li> </ul> <p><b>Indirect Financial Burden (Worker Productivity Loss):</b></p> <ul style="list-style-type: none"> <li>56% of patients had worked since their diagnosis and of these 53% had to decrease their hours</li> </ul>	N/A

Reference	Study Description	Study Design Setting/Data Source (Subjects, n)	Study Inclusion Criteria Participant Demographics	Financial Burden and Financial Distress Measures: Definition, Prevalence	Financial Toxicity Outcomes
Bolden and Wicks, 2010 (USA) <sup>35</sup>	To examine predictors of subjective burden and mental health status of family caregivers of persons with chronic liver disease	Cross-sectional University-based hepatology practice in a large southeastern US city, 2010 (n=73)	<ul style="list-style-type: none"> <li>Family caregivers of patients with chronic liver disease</li> <li>Mean caregiver age 48 y</li> <li>22% male</li> <li>66% White, 30% Black, 4% Other</li> <li>Average of 6 years providing informal caregiving</li> <li>38% of care recipients had cirrhosis</li> </ul>	<p><b>Psychological Financial Distress (Worry about Affording Healthcare, General Financial Anxiety):</b></p> <ul style="list-style-type: none"> <li>63% felt their financial status was significantly worse after the diagnosis of cirrhosis</li> </ul> <p><b>Indirect Financial Burden (Worker Productivity Loss):</b></p> <ul style="list-style-type: none"> <li>26% of caregivers had experienced a decrease in their income</li> <li>15% of caregivers were unemployed</li> </ul>	Caregivers who experienced a decrease in their income were more likely to report depressive and anxiety symptoms and caregiver burden
Serper et al., 2017 (USA) <sup>33</sup>	To evaluate the association of “medication trade-offs”—defined as choosing to spend money on other expenses over medications—with medication nonadherence and transplant outcomes	Cross-sectional Two large US transplant centers, 2011–2012 (n=103)	<p>Liver transplant recipients &gt; 30 days post-transplant</p> <ul style="list-style-type: none"> <li>51% 46–64 y</li> <li>58% male</li> <li>81% White, 14% Black, 6% Other</li> </ul>	<p><b>Indirect Financial Burden (Worker Productivity Loss):</b></p> <ul style="list-style-type: none"> <li>73% of liver transplant recipients were unemployed</li> </ul> <p><b>Behavioral Financial Distress (Tradeoffs for Healthcare, Tradeoffs for Necessities):</b></p> <ul style="list-style-type: none"> <li>17% of patients reported medication trade-offs; the most common trade-off was inability to afford a prescription in the past 12 months and making choices between prescriptions and food</li> </ul>	<p>Patients with trade-offs were more likely to report nonadherence to medications (mean adherence: 77 ± 23% with trade-offs vs. 89 ± 19% without trade-offs, p &lt; 0.01).</p> <p>The presence of medication trade-offs was associated with post-transplant hospital admissions (RR 1.64, 95% CI 1.14–2.35, p &lt; 0.01)</p>

Strategies and Future Directions to Mitigate Financial Burden and Financial Distress in Chronic Liver Disease Care

Table 2.

	Screening for Financial Burden and Distress	Health-System Strategies	Proposed Policy Changes and Future Directions
<b>Financial Burden</b>	<p><i>Identify High-Risk Populations</i></p> <ul style="list-style-type: none"> <li>• Unemployed</li> <li>• Low socioeconomic status</li> <li>• Underinsured or no insurance</li> <li>• Limited English Proficiency</li> <li>• Lower educational attainment</li> <li>• Lower health literacy</li> <li>• Hepatic encephalopathy</li> <li>• Hepatocellular carcinoma</li> <li>• Multimorbidity</li> <li>• Liver transplant candidates/recipients</li> </ul>	<ul style="list-style-type: none"> <li>• Deprescribing</li> <li>• Switching to generic formulations</li> <li>• Discussing lower-cost alternative approaches</li> <li>• Early referral to co-pay and prescription drug assistance programs</li> <li>• Interdisciplinary collaboration with pharmacists</li> <li>• Telehealth and hospital-at-home care models</li> <li>• Transportation and parking vouchers for clinic visits</li> <li>• Early referral of caregivers to local and national support programs</li> </ul>	<ul style="list-style-type: none"> <li>• Expanding insurance coverage for high-cost medications in chronic liver disease care</li> <li>• Value-based drug pricing</li> <li>• Legislation to expand paid family/medical leave and informal caregiving compensation</li> </ul>
<b>Financial Distress</b>	<p><i>Screen for Financial Distress</i></p> <ul style="list-style-type: none"> <li>• Single item: “Are you having difficulty paying for your medical care?”<sup>40</sup></li> <li>• American College of Physicians “Costs of Care Conversations” tools and financial screening questions<sup>42,43</sup></li> <li>• Comprehensive Score for Financial Toxicity (COST) measure<sup>41</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Early referral to social work services</li> <li>• Universal screening for financial distress during clinic visits</li> <li>• Routine costs of care conversations when developing treatment plans</li> </ul>	<ul style="list-style-type: none"> <li>• Financial navigation and assistance programs specific to chronic liver disease</li> <li>• Community health workers and patient navigators to maximize social support</li> <li>• Comparative effectiveness and cost effectiveness studies in hepatology to inform practice guidance</li> </ul>