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# Depression and Anxiety symptoms in Patients with Liver Cirrhosis Before, During and After the COVID-19 Pandemic: Prevalence and Impact on Hepatic Decompensation

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**Background:** The COVID-19 pandemic substantially increased the burden of anxiety and depression, particularly among patients with chronic diseases. However, data on the prevalence of these symptoms in patients with liver cirrhosis (LC) during and after the pandemic remain limited. We evaluated the prevalence of anxiety and depressive symptoms in LC patients before, during, and after the pandemic and assessed their impact on hepatic decompensation.

**Methods:** In this single-centre cohort study, consecutive inpatients with LC, inpatients without liver disease (non-LD) and hospital employees as healthy controls (HC) were recruited during three matched calendar windows: April–June 2019, 2020 and 2024. Symptoms of Depression and anxiety were assessed on admission using the Patient Health Questionnaire-4 (PHQ-4). Patients with a known psychiatric disease, alcohol misuse or acute alcoholic hepatitis were excluded. The 2020 LC cohort was followed for 12 months; the primary endpoint was hepatic decompensation requiring readmission.

**Results:** Of 978 patients screened, a total of n = 603 were included (294 LC [110/129/55]; 309 non-LD [104/101/104]), plus 153 HC; 47% were female, median age 61 years. In LC, a positive screen for depressive symptoms rose from 3.6% in 2019 to 25.4% in 2020 and returned to 3.5% in 2024; anxiety symptoms followed the same pattern (4.5%, 24.4% and 1.8%). During the pandemic both were more frequent in LC than in non-LD patients (25.4% vs. 3.9% and 24.4% vs. 3.8%; both $p < 0.005$) or in HC. Of 96 LC patients followed for 12 months, 29 (31%) developed hepatic decompensation. Depressive symptoms were associated with decompensation in univariable analysis (HR 2.23, 95% CI 1.13–4.40), after adjustment, only Child-Pugh score remained independently associated with the endpoint (HR 1.9, 95% CI 1.2–3.1).

**Conclusions:** The COVID 19 pandemic was associated with a marked increase in anxiety and depressive symptoms in patients with liver cirrhosis, whereas no comparable rise occurred in either control group. Depressive symptoms were associated with subsequent hepatic decompensation over the following year. Routine screening, using an easy to apply test, can help to identify patients at risk during future health care crises and therefore should enable preventive interventions in susceptible groups.

**Keywords:** COVID-19, liver cirrhosis, depression, anxiety, hepatic decompensation, PHQ-4

## 1. Background

The Coronavirus disease 2019 (COVID-19) pandemic, caused by SARS-Cov 2 virus, emerged at the end of 2019 and rapidly spread around the world, causing more than six million deaths by the end of 2023 [1]. Because of its high transmissibility and the initial lack of population immunity, healthcare systems around the world experienced immense strain in attempting to manage the surge of infected patients. Within the first phase of the outbreak, hospitals had to deal with a critical shortage of essential resources and medical personnel [2]. These challenges not only affected the care of COVID-19 patients but also hampered routine health care services and outpatient care [3].

The COVID-19 pandemic thus posed an unprecedented global public health challenge, not only due to its direct physiological consequences but also to its impact on mental health and psychological distress. For example, incidence of anxiety, depression and loneliness increased when lockdowns and social distancing measures were implemented in most countries to reduce viral transmission [4]. Furthermore, chronic diseases such as diabetes or respiratory disorders were not only associated with increased vulnerability to severe outcomes from SARS-CoV-2 infection but were also identified as risk factors for psychological distress during the pandemic [5].

Emerging evidence suggests that the COVID-19 pandemic has also increased psychological distress in patients with chronic liver disease (CLD) or liver cirrhosis (LC) [6]. These patients constitute a particularly vulnerable population due to their medical needs, including regular presentation to outpatient clinics or inpatient treatment for invasive procedures and monitoring.

LC patients are not only prone to develop liver related complications but also show a higher prevalence of mental illnesses compared to non-diseased patients [7]. In a multicentre study by Hernaez et al., including more than 1000 LC patients, rate of anxiety was more than 40% and one out of six patients suffered from severe depression [8]. Therefore it appears plausible that LC patients were particularly vulnerable to pandemic-related mental distress, but longitudinal data comparing the mental health status before, during, and after the pandemic remain limited. Furthermore, it remains unclear whether the onset of anxiety and depressive symptoms during the COVID-19 pandemic had a prognostic impact in terms of deteriorating liver function.

There are several potential mechanisms by which depressive symptoms could accelerate hepatic deterioration in cirrhosis. Depression is associated with reduced adherence to medication, diet and follow-up appointments, with reduced physical activity and progressive sarcopenia, and with relapse of alcohol consumption in patients with alcohol-related liver disease. Whether depressive symptoms

translate into a measurably higher risk of hepatic decompensation, however, has rarely been assessed prospectively.

Therefore, to assess the psychological impact of the COVID-19 pandemic on LC patients, we conducted a cohort study including patients who were hospitalized at the University Medical Center Hamburg-Eppendorf during the early phase of the pandemic (COVID cohort). The prevalence of anxiety and depression in this group was compared to two additional cohorts: one recruited before the onset of the COVID-19 pandemic and one after its official end, in order to enable a comparison of prevalence rates across different time periods. Moreover, patients in the COVID cohort were prospectively followed to assess subsequent hepatic decompensation.

## 2. Methods

### 2.1 Patients

Three cohorts of consecutive patients at different time points were analyzed. The COVID cohort (Cohort 2; cohorts were numbered chronologically) consisted of all eligible patients who presented to the University Medical Center between April 1st and June 30th, 2020. In addition, a total of n = 153 employees of the University Medical Center Hamburg-Eppendorf, none of whom had a history of chronic somatic or psychiatric disease, were enrolled as healthy controls (HC). HC were recruited exclusively during the pandemic period (cohort 2, April to June 2020) in order to compare LC patients, non-LD inpatients and healthy individuals at the same point in time. After the COVID-19 pandemic was officially declared over in April 2023, a post-COVID cohort (cohort 3) was recruited including all eligible inpatients admitted between April 1st and June 30th 2024. To ensure comparability across cohorts, patients who presented to the first Department of Medicine in the pre-COVID period from April to June 2019 were retrospectively analyzed (cohort 1; pre-COVID).

### 2.2 Baseline characteristics

The aetiology of LC was recorded and grouped into alcohol-related liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD; previously termed non-alcoholic fatty liver disease), and other chronic liver diseases (others). Aetiologies documented before 2023 were reclassified in accordance with the current steatotic liver disease nomenclature. Demographic characteristics and medical history were assessed by reviewing electronic medical records. Liver function impairment was graded according to the Child-Pugh score (CPS) and the Model for End-Stage Liver Disease (MELD) score. Inpatients without liver disease (non-LD) who were hospitalized during these three periods served as control group. The definition and recruitment of HC are described above.

## 2.3 Assessment of Depression and Anxiety

On admission, patients were screened for depression and anxiety using the PHQ-4 questionnaire as previously described [9]. The PHQ-4 combines two validated two-item subscales: the PHQ-2, covering the core symptoms of depression (anhedonia and depressed mood), and the GAD-2, covering the core symptoms of generalized anxiety (nervousness and uncontrollable worrying). Respondents rate how often they have been bothered by each symptom over the preceding two weeks on a four-point Likert scale ranging from 0 ("not at all") to 3 ("nearly every day"). Subscale scores range from 0 to 6, and the total score from 0 to 12, with higher values indicating greater symptom burden. According to the initial report by Kroenke et al. 9 , the following cut-off values were used:

- PHQ-2 subscale for depression: ≥ 3 indicates a positive screen for depressive disorder
- GAD-2 subscale for anxiety: ≥ 3 indicates a positive screen for anxiety disorder

Total score: 0–2 = normal, 3–5 = mild, 6–8 = moderate, 9–12 = severe psychological distress

The screening for depression and anxiety was part of the medical admission examination on the day the patient was admitted to the First Department of Medicine and was carried out by experienced nurses. For all patients who screened positive for depression or anxiety, a psychiatric consultation was arranged for further assessment. In the COVID cohort, all HC were screened after enrollment in April 2020.

## 2.4. Exclusion criteria

Patients who reported regular alcohol consumption, alcohol misuse or who were referred for alcohol-associated hepatitis were excluded from the study. In addition, patients with a known history of depression, psychiatric diseases or anxiety disorders, as well as those taking antidepressant or antipsychotic medications, were excluded from further analysis well as all patients with active malignant disease.

## 2.5. Follow up

Of the 129 LC patients in cohort 2, 95 were eligible for the 12-month follow-up. Patients were excluded from follow-up analysis if they died during the index hospitalization (n = 4), withdrew consent (n = 2), were lost to follow-up (n = 24), or were transferred to another institution (n = 4). Baseline characteristics of patients included and excluded from follow-up analysis did not differ significantly with respect to age, CPS stage, or prevalence of depression.

## 2.6 Statistical Analysis

Categorical variables were described in terms of percentages and frequencies; continuous variables were described in terms of median with minimum-to-maximum range. Decompensation-free survival

was estimated using the Kaplan–Meier method and compared between groups with the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox proportional hazards regression; the proportional hazards assumption was checked graphically using log-minus-log plots.

Univariable and multivariable logistic regression analyses were used to identify variables associated with a positive PHQ-4 screen for depressive or anxiety symptoms. Because of the limited number of events, the multivariable model for hepatic decompensation was restricted to a priori defined covariates. Subgroup analyses stratified by Child-Pugh stage and aetiology were exploratory and were not adjusted for multiple testing. Fisher's exact test was used to compare the distribution of categorical variables between groups. For continuous variables with normal distribution, t-test was used. Non-normal distributed variables were compared using the Mann-Whitney U test. The Kruskal-Wallis rank sum test was used to compare continuous variables across more than two groups. A two-sided p value $<0.05$ was considered statistically significant.

All statistical analyses were performed using GraphPad Prism 10.4 (GraphPad Software) and SPSS Statistics version 31 (IBM). The study is reported in accordance with the STROBE statement for observational studies.

### 2.7 Ethical approval

This study was approved by the Ethics Committee of the Medical Council of Hamburg (WF-052/20) in 2020. All patients and HC who were enrolled in the COVID cohort gave written informed consent prior to any study intervention. Patients in the pre- and post-COVID cohorts were retrospectively identified and analysed in anonymised form in accordance with local law (Hamburgisches Krankenhausgesetz).

### 2.8. Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used Claude (Anthropic)) to assist with language editing and improvement of readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

## 3. Results

A total of n= 978 inpatients were screened for eligibility, n= 603 inpatients were included in the final analysis: n= 294 with LC (cohort 1/2/3: n= 110/129/55), n= 309 without LD (cohort 1/2/3: n= 104/101/104). In addition, n= 153 HC were enrolled during the pandemic period, so that a total of 756 individuals were analyzed. The distribution of the three cohorts as well as number of excluded patients and reason for exclusion is depicted in **Figure 1.**

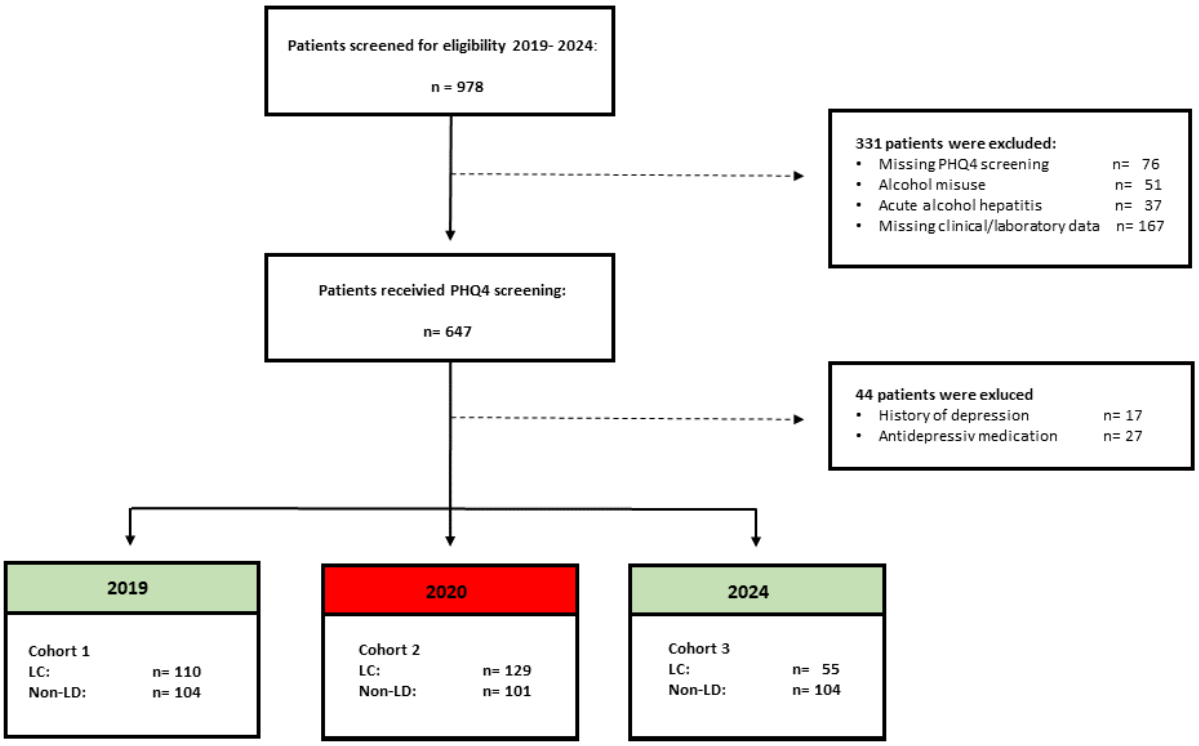



**Figure 1.** Flow chart of the study. A total of n = 978 patients were screened, n = 603 were finally included for further analysis. The presence of liver cirrhosis (LC) was assessed by reviewing the medical records. Three cohorts were established, comprising all eligible patients who presented between April 1st and June 30th of each respective year: pre-COVID cohort (2019), COVID cohort (2020), and post-COVID cohort (2024). Non-LD = no chronic liver disease.

The median age of all LC patients was 61 years (range: 18- 94) and n= 170 (58%) were male. The most prevalent underlying liver disease in LC patients was ALD (44%) followed by MASLD (10%) and various disease including chronic viral hepatitis B/C infection, autoimmune hepatitis, primary biliary cholangitis (44% in total). For the COVID cohort only, n= 153 HC were enrolled at the same time period in 2020; n= 113 (73%) were female, median age was 43 (21–61) years. Baseline demographic and clinic characteristics are depicted in **Table 1**.

Table 1. Caption: Demographic characteristics, diagnostic and laboratory findings of inpatients with and without liver cirrhosis and healthy controls

| | | 2019 | | 2020 | | | 2024 | |
|---|---|---|---|---|---|---|---|---|
| **Characteristics** | **All** | **LC** | **Non-LD** | **LC** | **Non-LD** | **HC** | **LC** | **Non-LD** |
| *n* | **756** | **110** | **104** | **129** | **101** | **153** | **55** | **104** |
| Sex: male (n; %) | 351; 58.2 | 68; 61.8 | 53; 51 | 61; 47.3 | 66; 65.5 | 40; 33 | 41; 74.5 | 62; 59.6 |
| Age (a; median, range) | 61; 18 - 94 | 63; 23 - 80 | 56; 18 - 94 | 69, 19-85 | 59; 20- 91 | 43; 21- 61 | 65; 20 - 88 | 66; 19 - 90 |
| **Etiology of LC (n;%)** | | | | | | | | |
| ALD | 128; 44 | 52; 47.3 | - | 64; 49.6 | - | - | 12; 21.8 | - |
| NAFLD/NASH | 30; 10 | 6; 5.5 | - | 20; 15.5 | - | - | 4; 7.3 | - |
| Other | 136;46 | 52; 47.3 | - | 45; 34.9 | - | - | 39; 70.9 | - |
| **Diagnosis on Admission (n;%)** | | | | | | | | |
| Acute pancreatitis | 6; 0.3 | - | 2; 1.9 | - | 1; 1.0 | - | - | 3; 2.9 |
| Chronic pancreatitis | 13; 0.7 | - | 4; 3.8 | - | 4; 4.0 | | - | 5; 4.8 |
| Abdominal infection | 10; 0.5 | - | 2; 1.9 | - | 6; 6.0 | - | - | 2; 1.9 |
| Tumor related | 73; 3.7 | - | 15; 14.4 | - | 27; 26.7 | - | - | 31; 29.8 |
| IBD | 17; 0.7 | - | 6; 5.8 | - | 8; 7.9 | - | - | 3; 2.9 |
| Other | 190; 9.6 | - | 75; 72.1 | - | 55; 54.5 | - | - | 60; 0.6 |
| **Lab values (median; range)** | | | | | | | | |
| Bilirubin [mg/l] | 1.4; 0.3 – 5.8 | 1.25; 0.4 – 5.6 | - | 1.5; 0.6 – 5.8 | - | - | 0.9; 0.6 – 5.2 | - |
| INR | 1.07; 0.5-5.9 | 1.2 ; 0.9 – 2.3 | - | 1.25; 1- 2 | - | - | 1.1; 0 – 1.5 | - |
| MELD | 11; 6 -29 | 11; 6 - 39 | - | 12; 6 – 26 | - | - | 10; 6 - 36 | - |
| **CPS** | 2 | 2 | - | 2 | - | - | 2 | - |

**Abbreviations:** ALD, alcoholic liver disease; BMI, Body Mass Index; CPS, Child-Pugh score; IBD, inflammatory bowel disease; INR, International Normalized Ratio; MELD, Model of end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

The prevalence of depressive symptoms in LC, non-LD and HC (cohort 2 only) patients was 3.6% vs. 2.8% ($p = 0.75$) in cohort 1, 25.4% vs. 3.9% vs. 3% ($p < 0.005$) in cohort 2 and 3.5% vs. 2.8% ($p = 0.81$) in cohort 3. The prevalence of anxiety symptoms was 4.5% vs. 1% ($p = 0.11$) in cohort 1, 24.4% vs. 3.9% vs. 5.8% ($p < 0.005$) in cohort 2 and 1.8% vs. 1.9% ($p = 0.9$) in cohort 3 (Figure 2).

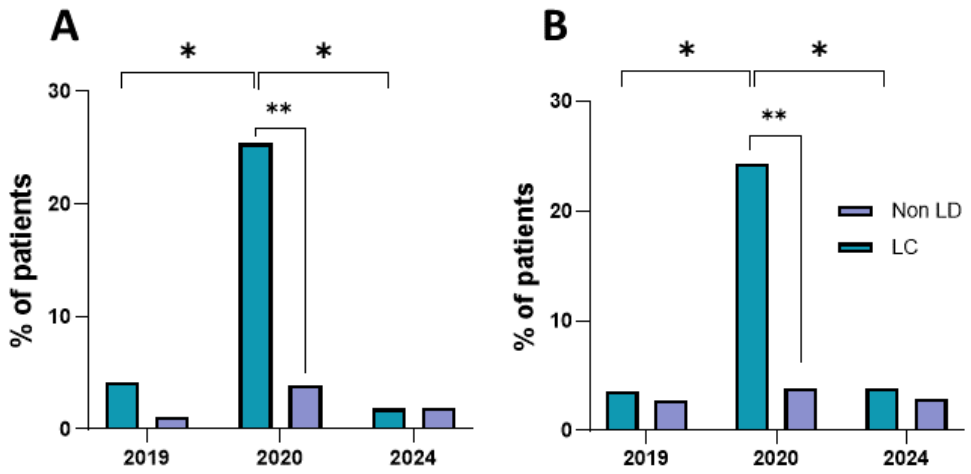



Figure 2. Prevalence of depressive symptoms (A) and anxiety symptoms (B) in patients with liver cirrhosis (LC) and in inpatients without liver disease (non-LD) before (2019), during (2020), and after (2024) the COVID-19 pandemic. Healthy controls (HC) were assessed during the pandemic period only.

In the subgroup analysis of LC patients stratified by CPS, the prevalence of depressive and anxiety symptoms differed significantly between the three periods in Child-Pugh A and B patients, but not in Child-Pugh C patients (see Figure 3).

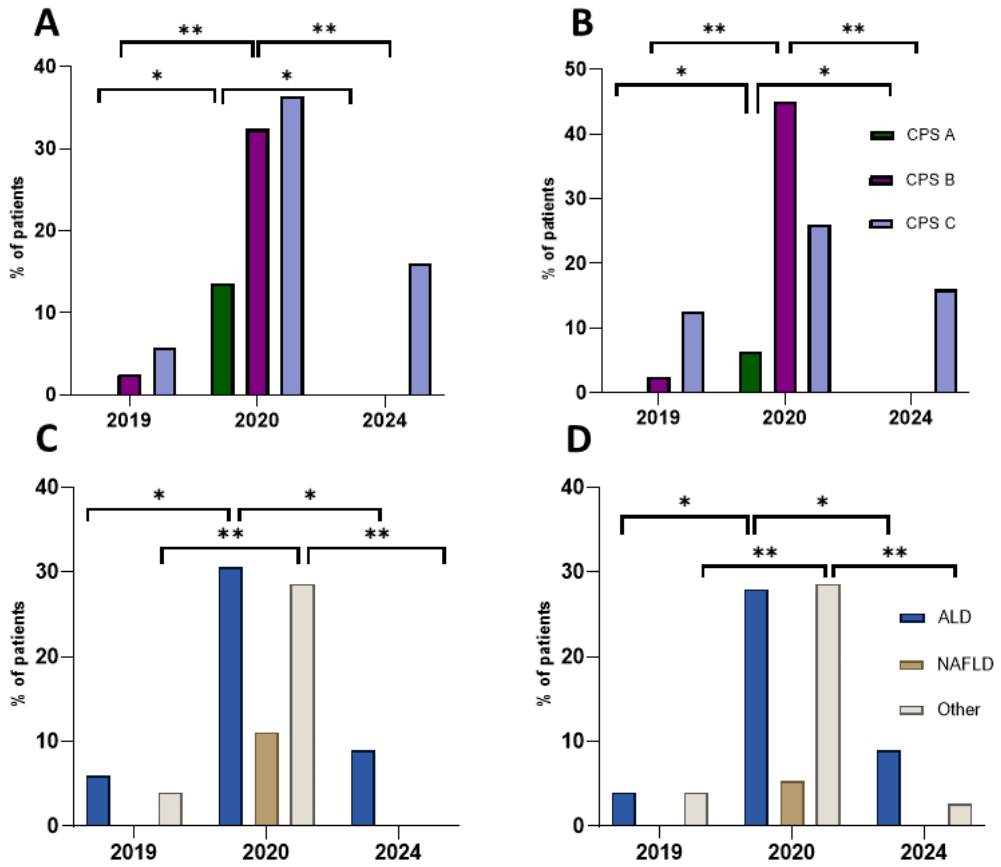



Figure 3. Prevalence of depressive symptoms (A) and anxiety symptoms (B) in LC patients according to the Child-Pugh Score (CPS; A-C). In the subgroup analysis of different aetiologies, depressive symptoms (C) were more prevalent in ALD patients, while anxiety symptoms showed the highest increase in patients with liver disease other than ALD or MASLD during the pandemic (D).

Among the LC patients, the prevalence of depressive symptoms in all CPS A patients over time (cohort 1/2/3) was 0%, 9.6%, and 0%, respectively (p = 0.027). In CPS B, prevalence rates were 2.6%, 45%, and 0% (p = 0.003), and in CPS C: 12.5%, 25%, and 16.6% (p = 0.714). The prevalence of anxiety symptoms also varied over time: in CPS A patients, it was (cohort 1/2/3) 0%, 13%, and 0% (p = 0.006); in CPS B: 2.6%, 32.2%, and 0% (p = 0.0027); and in CPS C: 6%, 36%, and 16.6% (p = 0.178). Overall, rate of depressive symptoms significantly increased in cohort 2 in CPS A and CPS B patients, whereas the increase in CPS C patients did not reach statistical significance.

Within each period, the prevalence of depressive and anxiety symptoms did not differ significantly between etiologies of liver cirrhosis: in cohort 1, depressive symptoms were numerically more frequent in patients with ALD-associated cirrhosis (ALD/MASLD/others): 6.1% vs. 0% vs. 4%; p = 0.76, in cohort 2, distribution was 30.6% vs. 11% vs. 28.6%; p = 0.42 and in cohort 3: 9% vs. 0% vs. 0% ;p = 0.16. In terms of anxiety symptoms, the distribution according to underlying liver disease was (ALD/MASLD/other): 4%

vs. 0% vs. 4% in cohort 1 (p = 0.88), 28% vs. 5.3% vs. 28.5% (p = 0.21) in cohort 2 and 9% vs. 0% vs. 2.6% (p = 0.59) in cohort 3. No significant differences were observed in the distribution of underlying liver disease etiologies across the three cohorts.

In patients with ALD associated cirrhosis, the prevalence of depressive symptoms increased significantly in 2020 compared to 2019 and decreased again in 2024: 6.1% vs. 30.6% vs. 9% (p = 0.023). In contrast, patients with MASLD showed no significant variation in depression prevalence across the three years: 0% vs. 11% vs. 0% (p = 0.585). Patients categorized under other chronic liver diseases demonstrated a sharp increase in depression cases in 2020, followed by a substantial decrease by 2024: 4% vs. 28.6% vs. 0% (p < 0.001), see Figure 3.

Anxiety symptoms showed a comparable time-dependent trend: Among patients with ALD cirrhosis, rates of anxiety were (2019/2020/2024): 4% vs. 28% vs. 9% (p = 0.015). Patients with liver disease other than ALD or MASLD showed a similar development: 4% vs. 28.5% vs. 2.6% (p = 0.0019). In MASLD patients, anxiety symptoms remained infrequent, with 5.3% in 2020 and no cases in 2019 or 2024 (Figure 3).

In a multivariable logistic regression model including gender, age, degree of liver cirrhosis according to CPS, aetiology of LC (ALD vs. non-ALD) and exposure to the pandemic period (i.e. belonging to cohort 2), only exposure to the pandemic period was a significant risk factor for the development of depressive symptoms (OR: 4.6, 95% CI:1.6- 17.2; p = 0.012). In terms of anxiety symptoms, higher age (OR: 1.05, 95% CI: 1.02- 1.11; p = 0.04) and belonging to cohort 2 (OR 6.4, 95% CI: 1.8–29.3; p = 0.006) were significant risk factors (Figure 4).

**A**

| Variable | OR | 95% CI | *p* |
|---|---|---|---|
| Gender | 1.03 | 0.307 – 3.555 | 0.96 |
| Age (a) | 0.92 | 0.927 – 1.024 | 0.27 |
| CPS | 0.95 | 0.946 - 3.018 | 0.06 |
| Alcoholic LD | 1.13 | 0.434 - 2.789 | 0.79 |
| **Exp. to SARS-CoV-2** | **4.06** | **1.160 – 17.271** | ***0.03*** |

**B**

| Variable | OR | 95% CI | *p* |
|---|---|---|---|
| Gender | 0.81 | 0.270 – 2.411 | 0.70 |
| **Age (a)** | **1.05** | **1.003 – 1.121** | **0.04** |
| CPS | 0.91 | 0.339 – 1.871 | 0.83 |
| Alcoholic LD | 1.13 | 0.434 - 2.789 | 0.79 |
| **Exp. to SARS-CoV-2** | **6.37** | **1.884 – 29.32** | ***0.006*** |

**Figure 4.** Multivariable logistic regression analysis for depressive symptoms (**A**) and anxiety symptoms (**B**) in LC patients. CPS, Child-Pugh Score; LD, liver disease; MELD, Model for end-stage liver disease.

A total of n= 96 patients of the COVID cohort were eligible for the 12-month follow-up; n= 41 were male, median age 61 years (range 33–81); n= 44 were CPS A, n= 35 CPS B and n= 17 CPS C.

During the follow-up period, n= 29 patients were readmitted to hospital due to acute hepatic decompensation, e.g. development of ascites or overt hepatic encephalopathy, and therefore met the primary endpoint. Among patients with decompensated liver function, the median time to decompensation was 114 days (d) in CPS A patients (range: 33- 365), 29 d in CPS B (range: 1- 274) and 27 d in CPS C patients (range: 7–207; p = 0.002). Decompensation was more frequent in patients with higher CPS (A/B/C): 13% vs. 40% vs. 52%; Log-Rank p = 0.002. The Cox regression hazard ratio (HR) was 3.65 (95% CI: 1.40–9.52; p = 0.008) for CPS B and 5.40 (95% CI: 1.91–15.25; p = 0.001) for CPS C patients. In patients with depressive symptoms, decompensation was significantly more frequent (51% vs. 30%; p = 0.017; HR 2.23, 95% CI: 1.13–4.40; p = 0.021). Kaplan–Meier curves are depicted in **Figure 5**.

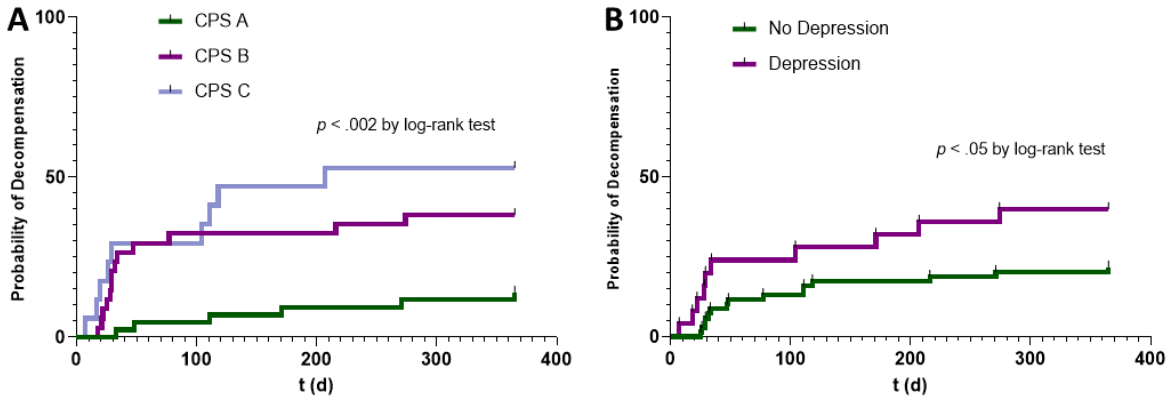



**Figure 5.** Kaplan–Meier analysis of hepatic decompensation in patients with liver cirrhosis (LC) from the COVID-19 cohort. Advanced liver disease (Child–Pugh stage C) was associated with a significantly increased risk of hepatic decompensation during the 12-month follow-up period (**A**). Similarly, patients with a positive screen for depressive symptoms exhibited a significantly higher risk of hepatic decompensation than those without (**B**).

In a Cox proportional hazards regression analysis including age, sex, CPS, anxiety and depressive symptoms, only higher CPS remained independently associated with hepatic decompensation (HR 1.9, 95% CI: 1.2–3.1). The association between depressive symptoms and decompensation observed in the univariable analysis was attenuated after adjustment and no longer reached statistical significance (HR 1.7, 95% CI: 0.7–4.0).

## 4. Discussion

In this study, depressive and anxiety symptoms were markedly more frequent in patients with liver cirrhosis during the COVID-19 pandemic than in the periods before and after it, and more frequent than in inpatients without liver disease or in healthy hospital employees assessed at the same time. Patients with a positive screen for depressive symptoms were also more likely to develop hepatic decompensation during the subsequent 12 months, although this association was attenuated and no longer statistically significant once liver function was taken into account.

It is known that depression and anxiety are common among LC- and CLD patients and significantly impair quality of life and functional status in affected patients. In a recent Danish study, Østberg et al. reported rates of 3% for depression and 15% for anxiety in LC patients [10]. Consistent with these findings, the prevalence of depressive symptoms observed in our pre-COVID and post-COVID cohort in LC patients was comparable, while the rate of anxiety was slightly lower. The observed difference may be due to the different screening tests used: while diagnosis in the study of Østberg et al. based on the Beck Anxiety Inventory (BAI), a 21-item questionnaire, the PHQ-4 was used in this study. The PHQ-4 includes two items specifically targeting anxiety, and despite its brevity, it has demonstrated comparable sensitivity to the more extensive 7-item Generalized Anxiety Disorder scale (GAD-7) [11, 12].

Following initial reports that mental health problems were more common in infected individuals, chronic disease has subsequently been identified as a specific risk factor for the development of anxiety and depression [13–15]. In our study, both anxiety and depressive symptoms increased significantly only among LC patients when compared to non-LD inpatients or healthy controls during the early months of the pandemic. This highlights the particular vulnerability of individuals with chronic liver disease to the development of mental health disorders. Of note, anxiety symptoms were also recorded in non-LD inpatients and in HC during the early phase of the pandemic. Because no pre-pandemic assessment of the HC group was performed, however, it cannot be determined whether these rates were elevated relative to their own baseline.

The pathogenesis of depression development in patients with chronic disease during the pandemic is a matter of debate: Annaswamy et al reported that patients with chronic diseases experienced higher levels of daily stress during the pandemic, as they were disproportionately affected by the shift from in-person medical care to telemedicine [16]. These patients often report greater unmet medical needs compared to individuals without chronic conditions and were more likely to face socioeconomic disadvantages and heightened fear of severe SARS-CoV-2 infection [17, 18]. Although our study cannot offer a detailed analysis due to the absence of these data, it is plausible that these factors similarly contributed to the increase in mental disorders observed in our cohort.

Santomauro et al. identified reports of daily SARS-CoV-2 infection rates and reduction in human mobility as significant risk factors for depression and anxiety onset during the pandemic [19]. Of note, in March 2020, when the incidence of COVID-19 began to rise in northern Germany and the first COVID-19-related deaths were reported, several local quarantine measures were implemented in the city of Hamburg. These measures ranged from closing of schools to a general lockdown decree at the end of March, resulting in prolonged social isolation. At the same time, the rate of virus spreading increased rapidly and for the first time more than 10,000 people were infected in northern Germany (Robert Koch Institute; www.rki.de; accessed 20 January 2026). These risk factors may explain the sharp increase in the incidence of depression and anxiety observed in all LC patients of the COVID cohort. However, here it remains unclear why the incidence of both conditions remained largely unchanged in the control group, despite being exposed to the COVID-19 pandemic at the same time.

Specifically in LC patients, several risk factors for depression and anxiety have been identified prior to COVID pandemic: In terms of depression, older age, widowhood and substance abuse have been described as significant risk factors [15, 20]. Regarding the degree of liver function impairment, depression has been reported to be more prevalent in patients with higher CPS or presence of ascites and more severe hepatic encephalopathy [21, 22]. Indeed, in our study, prevalence of depression significantly increased in CPS A patients and in CPS B patients in the COVID cohort, whereas the increase in CPS C patients did not reach statistical significance, possibly owing to the small number of patients in this stratum. In line with previous studies, the prevalence of depression was highest among patients with CPS C cirrhosis across all three cohorts, underscoring the association between advanced liver dysfunction and depressive symptoms.

In our study, only exposure to the pandemic period was a significant risk factor for both anxiety and depressive symptoms, while neither degree of liver function status nor etiology of cirrhosis reached significance in the multivariate analysis. With regard to anxiety, older age was also identified as a significant risk factor, although with a relatively modest odds ratio (OR) of 1.05 per year. These findings are consistent with the study by Akbulut et al. [23]. In this case-control study of more than 500 liver transplant recipients, exposure to COVID-19 was a strong risk factor for both conditions, again highlighting the vulnerability of patients with advanced liver disease to psychological distress.

In the prospectively followed COVID-19 cohort, depression, alongside the degree of liver dysfunction, was identified as an independent risk factor for rapid hepatic deterioration. Both parameters have previously been identified as relevant risk factors: the CPS is a well-established score for estimating the probability of death in LC patients and has been validated in a variety of studies since its first publication in 1964 23,24. Depression has also previously been described as a significant prognostic factor in LC patients [24].

It can only be speculated how depressive symptoms during the pandemic influenced liver function in LC patients. Studies addressing this issue are scarce. Increased alcohol consumption might have played a role: hospital admissions for alcohol-associated hepatitis increased during the first year of the pandemic, highlighting that there was a rapid increase in alcohol abuse possibly causing further deterioration of liver function in some LC patients [10, 25]. Of note, to minimize the effect of alcohol abuse, patients with alcohol-associated hepatitis, patients who excluded from all three cohorts of our study. Interestingly, the levels of both disorders returned to pre-pandemic values by 2024, after the WHO declared on 5 May 2023 that COVID-19 no longer constituted a Public Health Emergency of International Concern (PHEIC) [26]. The reasons for this decrease presumably relate to the vaccination program, improved understanding of the virus and its transmission, and declining overall infection rates [27, 28].

Our study has several limitations that need to be addressed. First, the PHQ-4 is an ultra-brief screening instrument for depressive and anxiety symptoms and does not establish a psychiatric diagnosis; all prevalence figures reported here therefore refer to positive screening results rather than to diagnosed disorders. The instrument also provides no information on the underlying mechanisms, so that we cannot determine which pandemic-related factors drove the observed increase. Second, only 29 decompensation events were observed among the patients followed, which limits the number of covariates that can reliably be entered into a multivariable model and renders the corresponding estimates imprecise. The association between depressive symptoms and decompensation was attenuated after adjustment for Child-Pugh stage, which is consistent both with confounding by liver function, since a positive screen was considerably more frequent at more advanced stages, and with insufficient power to detect an independent effect of this magnitude. Our data therefore do not allow these explanations to be distinguished, and the univariable association should be regarded as hypothesis-generating.

A notable limitation is the smaller sample size of the post-COVID cohort (cohort 3; n=55 LC patients) compared to cohorts 1 and 2 (n=110 and n=129, respectively). This imbalance is likely attributable to the broader implementation of outpatient management strategies and telemedicine services in the post-pandemic period, resulting in fewer hospitalizations during the recruitment window of April to June 2024. While this limits statistical power in cohort 3 subgroup analyses, particularly for CPS C patients, it does not preclude meaningful comparison of prevalence rates at a group level. Future studies should aim for prospective balanced recruitment to confirm the post-pandemic normalization observed in our data. Finally, a more important limitation concerns the comparability of the three recruitment periods. Between April and June 2020, elective admissions were largely suspended and the threshold for hospital admission was raised, so that the case mix of inpatients differed systematically from that in 2019 and 2024. Patients admitted during the pandemic period may therefore have been selected for greater

overall disease burden or psychosocial vulnerability, and part of the observed increase in symptom prevalence may reflect this shift rather than the pandemic itself. Although the distribution of Child-Pugh stages and MELD scores was comparable across the three periods, residual selection bias cannot be excluded.

But despite these limitations, our study documents a substantial increase in the prevalence of anxiety and depressive symptoms in LC patients during the COVID-19 pandemic, highlighting the psychological vulnerability of patients with chronic liver disease and the potential adverse consequences of the pandemic on their well-being.

## Conclusions

Taken together, patients with liver cirrhosis were particularly prone to depressive and anxiety symptoms during the COVID-19 pandemic when compared with inpatients without liver disease and with healthy hospital employees. Depressive symptoms were also associated with shorter decompensation-free survival, although this association did not persist after adjustment for Child-Pugh stage. Although the exact underlying mechanisms remain unclear, particularly since no prospective assessment of life circumstances, habits, or factors such as alcohol use was performed during the follow-up period, our study underscores the specific burden that health care crises place on patients with chronic liver disease. It further highlights the need for targeted psychosocial support and close monitoring of at-risk populations during such crises, and may help to inform patient care in future pandemics.

## List of abbreviations

| | |
|---|---|
| ALD | Alcohol-related liver disease |
| BAI | Beck Anxiety Inventory |
| CI | Confidence interval |
| CLD | Chronic liver disease |
| COVID-19 | Coronavirus disease 2019 |
| CPS | Child-Pugh score |
| GAD-2 | Generalized Anxiety Disorder-2 scale |
| GAD-7 | Generalized Anxiety Disorder-7 scale |
| HC | Healthy controls |
| HR | Hazard ratio |
| LC | Liver cirrhosis |
| MASLD | Metabolic dysfunction-associated steatotic liver disease |
| MELD | Model for End-Stage Liver Disease |
| non-LD | Inpatients without liver disease |
| OR | Odds ratio |
| PHEIC | Public Health Emergency of International Concern |
| PHQ-2 | Patient Health Questionnaire-2 |
| PHQ-4 | Patient Health Questionnaire-4 |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| WHO | World Health Organization |

## Declarations

**Ethics approval and consent to participate:** This study was performed in accordance with the Declaration of Helsinki and with local legislation (Hamburgisches Krankenhausgesetz), and was approved by the Ethics Committee of the Medical Council of Hamburg (Ethik-Kommission der Ärztekammer Hamburg; reference WF-052/20). Patients enrolled in the prospective cohort gave written informed consent prior to any study-related procedure. Retrospective analyses were performed on anonymised data in accordance with local legal requirements.

**Consent for publication:** Not applicable. The manuscript contains no data or images from which an individual participant could be identified.

**Availability of data and materials:** The datasets generated and analysed during the current study are not publicly available due to patient privacy and institutional data protection regulations, but are available from the corresponding author on reasonable request, subject to approval by the local ethics committee and applicable data protection requirements.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors' contributions:** TF and SP conceived the study and designed the protocol. GP, KH, TH and JK were responsible for patient recruitment and data acquisition. GP performed the statistical analysis, which was reviewed by TB and SP. GP and TF interpreted the data and wrote the first draft of the manuscript. TB, TH, KH, JK, SH, AL and SP revised the manuscript critically for important intellectual content. AL and SH supervised the project. TF is the guarantor of the study and had full access to all data. All authors read and approved the final manuscript.

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