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Clinical outcomes of COVID-19 in patients with liver cirrhosis - a propensity-matched analysis from a multicentric Brazilian cohort

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Abstract

Background Cirrhosis has been pointed out as a clinical entity that leads to worse clinical prognosis in COVID-19 patients. However, this concept is controversial in the literature. We aimed to evaluate clinical outcomes by comparing patients with cirrhosis to those without cirrhosis in a Brazilian cohort.

Methods Data from 20,164 COVID-19 inpatients were collected from 41 hospitals in Brazil between March to September 2020 and March 2021 to August 2022. We compared 117 patients with cirrhosis to 632 matched controls. A propensity score model was used to adjust for potential confounding variables, incorporating some predictors: age, sex at birth, number of comorbidities, hospital of admission, whether it was an in-hospital clinical manifestation of COVID-19, and admission year. Closeness was defined as being within 0.16 standard deviations of the logit of the propensity score.

Results The median age was 61 (IQR 50–70) years old, and 63.4% were men. There were no significant differences in the self-reported symptoms. Patients with cirrhosis had lower median hemoglobin levels (10.8 vs. 13.1 g/dl), lower platelets (127,000 vs. 200,000 cells/mm3), and leukocyte counts, as well as lower median C-reactive protein (63.0 vs. 76.0 $p=0.044$) when compared to controls. They also had higher mortality compared to matched controls (51.3% vs. 21.7%, $p<0.001$). They also had higher frequencies of admission in an intensive care unit (51.3% vs. 38.0%, $p=0.007$),

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invasive mechanical ventilation (43.9% vs. 26.6%, $p < 0.001$), dialysis (17.9% vs. 11.1%, $p = 0.038$), septic shock (23.9% vs. 14.9%; $p = 0.015$) and institution of palliative care (19.7% vs. 7.4%; $p < 0.001$).

Conclusions This study has shown that COVID-19 inpatients with cirrhosis had significantly higher incidence of severe outcomes, as well as higher frequency of institution of palliative care when compared to matched controls. Our findings underscore the need for these patients to receive particular attention from healthcare teams and allocated resources.

Keywords COVID-19, Liver cirrhosis, Patient Outcome Assessment, Propensity score, Cohort studies

Background

Liver cirrhosis has a variable prognosis and is associated with a rising global burden of morbidity and mortality. Its prevalence has approximately doubled since the 1990s. Epidemiological data related to chronic liver disease are variable and scarce, particularly in low-income countries, suggesting that the actual numbers may be underestimated [1]. Despite these limitations, some data indicate that cirrhosis is the eighth leading cause of death in Brazil, representing a significant disease burden [2].

During the COVID-19 pandemic, SARS-CoV-2 infection emerged as a major trigger of acute-on-chronic liver failure (ACLF), with studies consistently showing worse prognosis and higher mortality among patients with cirrhosis [3–5]. Cirrhosis has been established as an independent risk factor for mortality in COVID-19 patients, with more advanced liver disease correlating with increased mortality risk [6]. Notably, in a large North American cohort, full vaccination has shown to reduce mortality in patients with cirrhosis [7].

COVID-19 complications extend beyond the respiratory tract, affecting the cardiac, gastrointestinal, hepatic, renal, hematologic, and nervous systems [8–10]. Among patients with these complications, liver injury, indicated by elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), has been reported in a significant number of hospitalized COVID-19 patients, potentially indicating a poorer prognosis [11]. Direct liver damage by SARS-CoV-2 has been identified as one of the main factors contributing to ACLF and systemic inflammation in patients with pre-existing cirrhosis [12].

This study fills a significant gap in the understanding of COVID-19 outcomes in patients with cirrhosis in Latin America, where robust data are lacking. Up to September 2024, Brazil reached almost 39 million confirmed cases, with over 700,000 deaths due to COVID-19 complications [13]. However, it remains underrepresented in global research.

Therefore, this study aimed to compare the clinical features and outcomes of COVID-19-infected Brazilian inpatients with and without cirrhosis across different phases of the pandemic. This research addresses a gap in understanding this issue within the Brazilian population, which comprises approximately 49% of South America's population. By focusing on this population, our study contributes valuable insights that are essential for improving clinical care and resource allocation in the region, particularly for high-risk groups such as cirrhotic patients.

Materials and methods

Study design and participants

This study is part of a large multicenter retrospective Brazilian cohort (Brazilian COVID-19 Registry), which involved 41 hospitals, including private and public, in 18 cities from six Brazilian states (Bahia, Minas Gerais, Pernambuco, Rio Grande do Sul, Santa Catarina, São Paulo), comprising two periods: March to September 2020 and March 2021 to August 2022 [14].

This study included consecutive adult patients (≥ 18 years old) with laboratory-confirmed COVID-19 admitted to the participating hospitals. Positive cases were considered through the detection of SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR) tests in nasopharyngeal or oropharyngeal swab or serological tests [IgM] in the first phase of the study; and by RT-PCR in the second phase [14, 15]. Patients admitted because of COVID-19 or those who developed first symptoms of COVID-19 infection during hospitalization and tested positive were included. Patients transferred from other hospitals, those younger than 18, and pregnant and puerperal women were excluded from the present analysis.

Patients who reported having cirrhosis and had this comorbidity documented in their medical records were classified as "cases".

Data collection

Demographic data, clinical characteristics, laboratory results in hospital presentation, and outcomes were collected from the medical records by trained healthcare professionals and medical or nursing students to the Research Electronic Data Capture (REDCap®) electronic platform [16, 17], hosted at the Telehealth Center of the University Hospital of the *Universidade Federal de Minas Gerais* [18]. To ensure reliability and monitor data quality, the database was routinely audited. Study protocol and definition details were published elsewhere [16, 17]. For more details about the collected data, refer

to Supplementary File 1. All clinical data regarding the patient's previous history were considered based on the records in the medical register.

The Model for End-stage Liver Disease (MELD) score [19, 20] was calculated for patients with cirrhosis using data available from their medical records. No information about the stage of cirrhosis, the etiology or laboratory, imaging, or anatomopathological confirmation has been collected, as these data were not consistently available in the medical records.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included length of hospital stay, admission to the intensive care unit (ICU), invasive mechanical ventilation (IMV), renal replacement therapy, septic shock, nosocomial infection, acute heart failure, myocarditis, any type of bleeding, venous thromboembolism (VTE) and palliative care reference.

Statistical analysis

To mitigate potential confounding variables, a rigorous propensity score matching (PSM) approach was employed to balance the baseline characteristics between patients with underlying cirrhosis and control patients (those without underlying cirrhosis). The PSM model was estimated by logistic regression, incorporating a comprehensive set of predictors: age, sex at birth, number of comorbidities (hypertension, diabetes mellitus, obesity, coronary artery disease, heart failure, atrial fibrillation or flutter, chronic obstructive pulmonary disease, cancer, and previous stroke), hospital of admission, whether it was an in-hospital clinical manifestation of COVID-19 and admission year (2020 vs. 2021–2022) [14]. This robust model ensures a meticulous adjustment for these potential confounders.

Matching was conducted by identifying control group individuals whose propensity scores closely aligned with those of the cirrhotic patient group. Closeness was stringently defined as being within 0.16 standard deviations of the logit of the propensity score, which was measured on a scale from 0 to 1.00. This matching process was executed using the MatchIt package in R software.

Following the matching process, a thorough descriptive analysis of data was performed. Categorical data were presented as absolute numbers and proportions. The Kolmogorov-Smirnov test was applied to verify data normality. All continuous variables had non-normal distribution and were expressed as median and interquartile ranges (IQR). The chi-square and Fisher's exact tests were used to compare the distribution of categorical variables, while the Wilcoxon–Mann–Whitney test was used for continuous variables.

A subanalysis was conducted on all patients who had received at least one vaccine dose to compare hospital mortality between those with and without cirrhosis. Due to a large amount of missing data and the small number of vaccinated patients, this analysis was performed on the entire unmatched sample to preserve statistical power.

Statistical analysis was performed using R software (version 4.0.2) with tidyverse, stringr, gtsummary and MatchIt packages. Statistical tests were conducted with an alpha level of 0.05 in two-sided tests, so results were considered statistically significant if p-value was < 0.05.

Ethics statement

This study was approved by CONEP (Comissão Nacional de Ética em Pesquisa - National Research Ethics Committee - Certificate of Presentation for Ethical Assessment 30350820.5.1001.0008). Individual informed consent was waived by Comissão Nacional de Ética em Pesquisa - National Research Ethics Committee due to the pandemic situation and the use of data from medical records. This study had internal approval of ethics boards from each hospital. The study adhered to the Declaration of Helsinki.

Results

Demographic and clinical features

The study included 749 patients. Of those, 117 patients had cirrhosis and 632 were matched controls (Fig. 1). The median age was 61 (IQR 50–70) years old, and 63.4% were men. Regarding the diagnostic methods for COVID-19, in 97.5% of patients, the diagnosis was confirmed using RT-PCR for SARS-CoV-2, while in 2.5% it was confirmed using IgM for SARS-CoV-2 ($p = 0.753$).

Both groups had similar demographic characteristics and comorbidities, except for hypertension and chronic kidney disease (CKD) – people with cirrhosis had a lower frequency of hypertension (40.2% vs. 57.6%; $p < 0.001$) and a higher frequency of CKD (14.5% vs. 6.6%; $p = 0.004$) when compared to their matched controls. Smoking (14.5% vs. 5.1%, $p < 0.001$) and alcohol consumption (42.7% vs. 8.4%, $p < 0.001$) were more frequent in the cirrhosis than in the control group. Other demographic characteristics are shown in Table 1.

Patient's data upon hospital presentation

There were no significant differences in the self-reported symptoms between patients with cirrhosis and controls (Table S1). Regarding objective changes in signs on physical examination upon hospital presentations, a higher incidence of abnormal mental status, with Glasgow Coma Scale of less than 15, was noted in the study group (16.2% vs. 8.4%, $p = 0.008$). Regarding hemodynamic status, the group with cirrhosis had lower arterial pressure compared to the control group. This was evaluated using

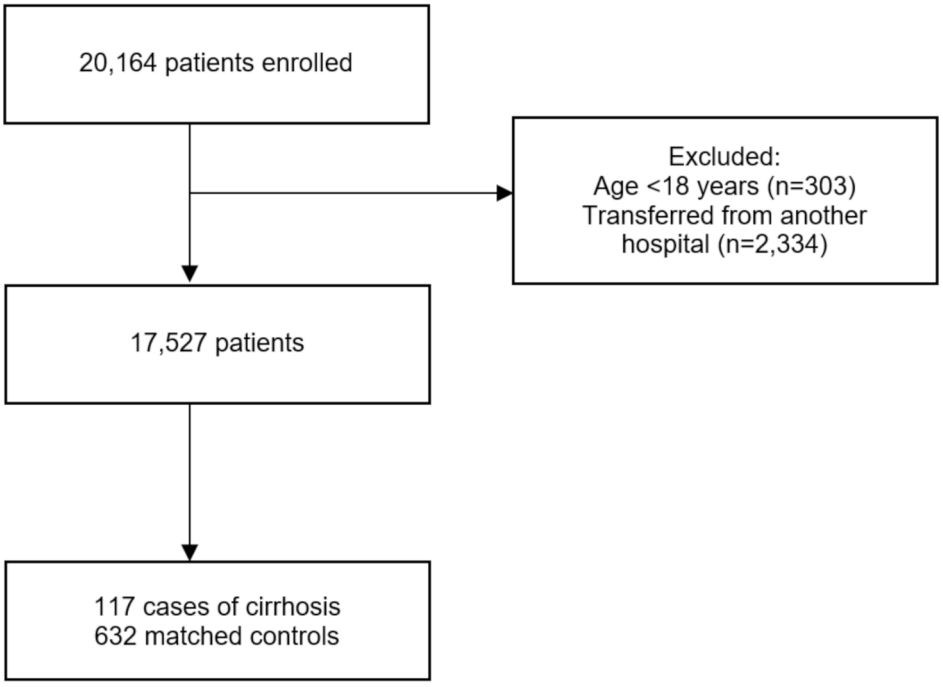

Fig. 1 Flowchart of the patients included in this study

Table 1 Demographics and clinical characteristics of Covid-19 patients with cirrhosis and matched controls without cirrhosis

Variables	Overall[1] *N* = 749	Study group[1] *N* = 117	Control group[1] *N* = 632	*p*-value[2]
Age (years)	61.0 (50.0, 70.0)	61.0 (52.0, 70.0)	61.0 (49.0, 70.0)	0.469
Sex (male)	475 (63.4%)	80 (68.4%)	395 (62.5%)	0.225
Hypertension	411 (54.9%)	47 (40.2%)	364 (57.6%)	< 0.001
CAD	52 (6.9%)	8 (6.8%)	44 (7.0%)	0.961
Heart Failure	59 (7.9%)	12 (10.3%)	47 (7.4%)	0.298
Atrial fibrillation	26 (3.5%)	5 (4.3%)	21 (3.3%)	0.583
Ischemic stroke	32 (4.3%)	2 (1.7%)	30 (4.7%)	0.209
Chagas disease	9 (1.2%)	0 (0.0%)	9 (1.4%)	0.368
Asthma	42 (5.6%)	5 (4.3%)	37 (5.9%)	0.495
COPD	51 (6.8%)	12 (10.3%)	39 (6.2%)	0.107
Diabetes mellitus	232 (31.0%)	43 (36.8%)	189 (29.9%)	0.141
Obesity	93 (12.4%)	13 (11.1%)	80 (12.7%)	0.641
CKD	59 (7.9%)	17 (14.5%)	42 (6.6%)	0.004
Rheumatologic conditions	20 (2.7%)	0 (0.0%)	20 (3.2%)	0.057
HIV infection	13 (1.7%)	2 (1.7%)	11 (1.7%)	> 0.999
Cancer	57 (7.6%)	12 (10.3%)	45 (7.1%)	0.240
Previous transplantation	12 (1.6%)	3 (2.6%)	9 (1.4%)	0.413
Illicit drugs use	14 (1.9%)	2 (1.7%)	12 (1.9%)	> 0.999
Alcohol abuse	103 (13.8%)	50 (42.7%)	53 (8.4%)	< 0.001
Current Smoking	49 (6.5%)	17 (14.5%)	32 (5.1%)	< 0.001
Previous smoker	135 (18.0%)	23 (19.7%)	112 (17.7%)	0.617

CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus [1]n (%); Median (IQR); [2] Statistical tests performed: chi-square test; Wilcoxon rank-sum test; Fisher's exact test

systolic blood pressure as a categorical variable (≥ 90 mmHg, adjusted for inotropic requirement), with 87.9% of the cirrhosis group meeting this criterion versus 95.4% of the control group ($p = 0.008$) (Table S1).

Regarding laboratory exams, patients with cirrhosis had lower median hemoglobin levels (10.8 g/dl vs. 13.1 g/dl; $p < 0.001$), lower platelets (127,000 cells/mm3 vs. 200,000 cells/mm3; $p < 0.001$), leukocytes, neutrophils,

Table 2 Laboratory exams of Covid-19 patients with cirrhosis and matched controls without cirrhosis upon hospital presentation

Variables	Overall[1] *N* = 749	Control group[1] *N* = 632	Study group[1] *N* = 117	*p*-value[2]
Hemoglobin (g/dL)	12.7 (10.9, 14.3)	13.1 (11.4, 14.4)	10.8 (8.9, 12.4)	< 0.001
Leukocytes (cells/mm^3)	7,300.0 (5,335.0, 10,292.5)	7,440.0 (5,630.0, 10,410.0)	6,026.0 (3,810.0, 9,410.0)	< 0.001
Neutrophils (cells/mm^3)	5,430.0 (3,732.0, 8,089.5)	5,481.0 (3,940.0, 8,159.0)	4,347.0 (2,631.2, 7,202.8)	< 0.001
Lymphocytes (cells/mm^3)	1,020.0 (680.0, 1,530.0)	1,080.0 (727.5, 1,549.2)	850.5 (496.5, 1,306.5)	< 0.001
Platelets (cells/mm^3)	194,000 (143,000, 258,000)	200,000 (156,500, 262,000)	127,000 (73,250, 203,750)	< 0.001
Total bilirubin (mg/dL)	0.6 (0.4, 0.9)	0.5 (0.3, 0.7)	1.2 (0.7, 2.3)	< 0.001
aPTT (seconds)/control	1.0 (1.0, 1.2)	1.0 (1.0, 1.1)	1.1 (1.0, 1.4)	< 0.001
INR	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.3 (1.2, 1.6)	< 0.001
Creatinine (mg/dL)	0.9 (0.7, 1.3)	0.9 (0.7, 1.3)	1.0 (0.7, 1.5)	0.155
Urea (mg/dL)	39.0 (28.0, 60.3)	38.0 (28.5, 58.0)	44.0 (26.5, 75.0)	0.321
C-reactive protein (mg/L)	74.3 (38.0, 136.2)	76.0 (39.4, 137.8)	63.0 (24.4, 104.4)	0.044
Lactate (mg/dL)	1.6 (1.1, 2.1)	1.5 (1.1, 2.0)	2.0 (1.5, 2.7)	< 0.001
Aspartate aminotransferase (U/L)	43.0 (29.6, 73.0)	41.0 (28.0, 63.0)	60.0 (36.2, 116.9)	< 0.001
Alanine aminotransferase (U/L)	33.0 (21.0, 59.5)	33.0 (21.0, 63.0)	32.0 (20.0, 47.0)	0.242
Bicarbonate (mEq/L)	23.0 (20.1, 25.0)	23.0 (21.0, 25.1)	21.4 (17.2, 23.5)	< 0.001
pH	7.4 (7.4, 7.5)	7.4 (7.4, 7.5)	7.4 (7.4, 7.5)	0.693

aPTT: activated partial thromboplastin time; INR: international normalized ratio; [1]Median (IQR); [2]Statistical tests performed: Chi-square test; Wilcoxon rank-sum test; Fisher's exact test

Table 5 Clinical outcomes of the Covid-19 patients with cirrhosis and matched controls without cirrhosis during hospitalization

Variables	Overall[1] *N* = 749	Study group[1] *N* = 117	Control group[1] *N* = 632	*p*-value[2]
Hospital length of stay	10.0 (5.0, 20.0)	13.0 (6.0, 21.0)	10.0 (5.0, 20.0)	0.106
Admission in ICU	300 (40.1%)	60 (51.3%)	240 (38.0%)	0.007
Invasive mechanical ventilation	215 (29.3%)	50 (43.9%)	165 (26.6%)	< 0.001
Renal replacement therapy	91 (12.2%)	21 (17.9%)	70 (11.1%)	0.038
Septic shock	122 (16.3%)	28 (23.9%)	94 (14.9%)	0.015
Nosocomial infection	130 (17.4%)	27 (23.1%)	103 (16.3%)	0.078
Acute heart failure	19 (2.5%)	2 (1.7%)	17 (2.7%)	0.753
Myocarditis	4 (0.5%)	0 (0.0%)	4 (0.6%)	> 0.999
Bleeding	32 (4.3%)	8 (6.8%)	24 (3.8%)	0.139
VTE	35 (4.7%)	1 (0.9%)	34 (5.4%)	0.033
Palliative care	70 (9.4%)	23 (19.7%)	47 (7.4%)	< 0.001
In-hospital mortality	197 (26.4%)	60 (51.3%)	137 (21.7%)	< 0.001

ICU: intensive care unit; VTE: venous thromboembolism. [1]n (%); Median (IQR); [2]Statistical tests performed: chi-square test; Wilcoxon rank-sum test; Fisher's exact test

and lymphocytes counts, and lower median C-reactive protein (63.0 vs. 76.0 $p = 0.044$) when compared to controls. Median bilirubin activated partial thromboplastin time, international normalized ratio, and lactate levels upon hospital presentation were significantly higher in the cirrhosis group (Table 2). AST was abnormal in both groups, but the group with cirrhosis had a higher elevation than the controls (65.2 U/L vs. 42.0 U/L; $p < 0.001$). Among 117 patients with cirrhosis, 70 had enough data to calculate MELD score, with a median of 11.392 (IQR 7.029–18.046).

Outcomes analysis

In-hospital mortality was higher among patients with cirrhosis (51.3% vs. 21.7%, $p < 0.001$), compared to matched controls. They also had a higher frequency of ICU admission (51.3% vs. 38.0%, $p = 0.007$), IMV (26.6% vs. 43.9%, $p < 0.001$), dialysis (17.9% vs. 11.1%, $p = 0.038$), and septic shock (23.9% vs. 14.9%; $p = 0.015$). Additionally, they were referred to palliative care more often than the control group (19.7% vs. 7.4%; $p < 0.001$). On the other hand, patients with cirrhosis had a lower incidence of VTE when compared to the controls (0.9% vs. 5.4%; $p = 0.033$), and the incidence of hemorrhages was similar in both groups (6.8% vs. 3.8%; $p = 0.139$). The median length of stay was 10 days for the control group and 13 days for the cirrhosis group ($p = 0.106$) (Table 3).

In the subanalysis of patients who died and received at least one vaccine dose, 369 (21.1%) belonged to the control group, and 9 (52.9%), to the case group ($p = 0.004$). Details about the doses and types of vaccinations in both groups are provided in Table S2.

Discussion

This study found a high mortality rate of 51.3% among inpatients with liver cirrhosis and COVID-19, compared to 21.7% in the control group without cirrhosis. We also observed a higher frequency of other adverse outcomes in patients with cirrhosis, including intensive care admission, renal replacement therapy, nosocomial infection, and VTE, as well as a longer length of stay when compared to matched controls. Furthermore, patients with cirrhosis were more frequently referred for palliative care.

These findings align with previous research, like a cohort conducted in the early phase of the pandemic in the United States, which reported a relative risk (RR) of 4.6 for death in patients with cirrhosis and COVID-19 [21]. Our study showed a RR of 2.36 in comparison to patients without cirrhosis. A large cohort of hospitalized and non-hospitalized veteran affairs demonstrated higher hospitalization and mortality rates in patients with cirrhosis overall, but there was no significant difference in mortality between hospitalized subgroups [21]. Other studies have highlighted worse outcomes for patients with cirrhosis in the early stages of the pandemic before widespread vaccination [5, 22–26]. Our findings build on previous research, demonstrating that despite vaccination efforts, which have been shown to reduce mortality in patients with cirrhosis, individuals with cirrhosis continue to have a worse prognosis compared to those without cirrhosis.

An important strength of our study is the use of PSM, which effectively minimized important confounding factors such as age, sex, comorbidities, and the timing of the pandemic. Previous studies with similar aims also used PSM models, but they did not find a worse prognosis among patients with cirrhosis when compared to matched controls. This was likely due to smaller sample sizes, limiting statistical power, and by including patients from the earlier stages of the pandemic [3, 27].

Our study adds to this evidence by featuring a higher incidence of other severe outcomes than patients without cirrhosis, including ICU admission, septic shock, dialysis, respiratory failure, and IMV. The MELD score was calculated using available laboratory data, which were recorded in most cases. Despite the high mortality among patients with cirrhosis, we found that the median MELD score was low. Other important strengths of our study are the large number of inpatients with cirrhosis, and the period during which patients were included, as it crossed different phases of the pandemic, providing more representative data on the behavior of those patients. Furthermore, Latin American patients were underrepresented in previous studies, and our research contributes to a better understanding of the behavior of patients with cirrhosis in low-income countries.

In the present study, the status of decompensation or Child-Pugh were not consistently available in the medical records, so they could not be included in the analysis. Other studies have yielded notable findings. A multinational cohort study of COVID-19 outpatients and inpatients included 386 patients with cirrhosis, all of whom required hospitalization. A PSM model was used for each stage of cirrhosis in comparison to patients without cirrhosis. They found a mortality rate of 32% in the group with cirrhosis, compared to 8% in the group without cirrhosis ($p < 0.001$). In the analysis by Child-Pugh stage, no significant difference in mortality was noted for patients classified as Child-Pugh A compared to the group without liver cirrhosis. However, the mortality rate increased with the severity of underlying liver cirrhosis [3].

Another large cohort, of all adult inpatients with COVID-19 in France in 2020, also demonstrated that patients at different stages of liver disease may have varied responses. Using logistic regression analysis, it was found that patients with decompensated cirrhosis had a significantly higher mortality rate, while those with mild liver disease or compensated cirrhosis were not at increased risk of COVID-19-related death [6].

Our study was designed to evaluate all-cause hospital mortality and other outcomes, so it was not possible to determine specific causes of death. However, several factors may have contributed to the increased mortality in patients with cirrhosis. One of the non-liver-related factors is the increased incidence of CKD in the case group since it is well-known that renal impairment in patients with COVID-19 can lead to worse outcomes [27, 28]. Furthermore, the higher incidence of smoking in the study group compared to the control group might also have contributed to the increased mortality. Despite controversial studies about the relationship between smoking and COVID-19 outcomes, several studies have demonstrated an increase in the risk of hospitalization and mortality among smokers [29–31]. Smoking-related chronic lung disease has been identified as a contributing factor to worse prognosis in these patients [32]. In addition, we observed that respiratory failure occurred more frequently in patients with cirrhosis in line with previous data, which suggests that it remains the leading cause of death among that group of patients [3]. Lastly, patients with cirrhosis who become infected are prone to developing multiorgan failure, attributed mostly to the systemic inflammatory response syndrome (SIRS), which is associated with high mortality [3]. Patients with cirrhosis frequently present with systemic inflammation and immune deficiency, both of which are components of cirrhosis-associated immune dysfunction syndrome. This combination of inflammation and immune dysregulation is now believed to be a central pathophysiological mechanism in the natural history of cirrhosis [33]. Systemic

inflammation has traditionally been assessed using SIRS, which has been linked to poorer outcomes in patients with decompensated cirrhosis [34]. The presence of SIRS has also been shown to predict the development of portal hypertension-related complications and mortality in patients with cirrhosis experiencing acute decompensation [35]. Therefore, the increase in systemic inflammation caused by COVID-19 may further decompensate cirrhosis, increasing mortality, particularly in patients with more advanced stages of the disease.

Cirrhosis is a prevalent disease in Brazil, especially alcohol-related liver cirrhosis [36]. In the current study, it is not possible to establish a direct relationship between alcohol consumption and poorer outcomes due to the study's design. However, data from an international cohort [3] demonstrated that in a chronic liver disease group, alcoholic liver disease is an independent risk factor for COVID-19 mortality. Additional evidence from a study conducted on the North American population indicated an increase in alcohol consumption during the COVID-19 pandemic and a rise in cirrhosis-related deaths [37]. This finding is consistent with our data, which shows higher alcohol consumption prevalence among cases. Alcohol intake has been associated with multisystem involvement, including increased susceptibility to infections, which may contribute to poor prognosis [37].

Liver-related factors could also contribute to higher mortality among patients with cirrhosis. It is well known that those patients can develop ACLF when hospitalized, which is related to a poor prognosis [38, 39]. Moreover, patients with cirrhosis, mainly advanced cirrhosis, suffer from malnutrition and sarcopenia [40].

In our study, a higher number of patients with cirrhosis were eligible for palliative care than in the control group. This observation likely reflects the severity of ACLF in these patients. As a large number of cirrhotic patients often necessitated intensive care interventions, we suppose that there was a delay in the transition to palliative care and the limitation of life-sustaining treatments. This delay in palliative care referral could have contributed to the over-intervention observed in the cirrhosis group, underscoring the importance of timely and proactive palliative care management in this vulnerable population during acute illness episodes.

Our data showed higher mortality in both groups compared to most previous studies as cited above. There are several possible explanations for these findings. First, Brazil was one of the countries with the highest COVID-19 mortality rates [41]. Currently, Brazil ranks second in the number of COVID-19 deaths reported to the WHO [42]. During the COVID-19 pandemic, Brazil faced a severe health crisis, which has been documented in numerous publications [43, 44]. The contributing factors range from political decisions and stances [41] to inadequate technical preparation of healthcare professionals and a lack of financial resources.

In the first phase of our study (March to September 2020), 17 public hospitals from the Unified Health System (*Sistema Único de Saúde*, SUS) and 19 private hospitals were included. Eight of the latter had more than 50% of their beds allocated to SUS patients. In the second phase (March 2021 to August 2022),13 public hospitals and 11 private hospitals were included, four of which had more than 50% of their beds reserved for SUS patients. This is an important point, as SUS users generally faced greater difficulties accessing hospital beds during the pandemic and tended to have more decompensated comorbidities. In our study, they represented the majority of the population included.

Moreover, a recent epidemiological study showed that the death rate from cirrhosis in Brazil increased between 1996 and 2020 [45]. In 2020, the mortality rate was 18%, and the age-adjusted death rate was much higher compared to most European countries, being similar to that of the United States. Therefore, the high mortality rate among patients with cirrhosis alone may have contributed to our findings of increased mortality [45].

Studies on COVID-19 patients with underlying cirrhosis are scarce in Latin America. Thus, data from this study can help clinical professionals better understand the characteristics of COVID-19 in this population.

However, this study has some limitations. Due to the study's retrospective nature, patients were identified as having cirrhosis if it was mentioned during medical care and recorded in their medical files. We did not confirm diagnosis with imaging methods due to Brazil's lack of interconnected health record systems. Our statistical analysis did not account for the clinical behavior given the different strains prevalent at various phases of the pandemic (including the impact of vaccination). Additionally, the stage of liver disease, the etiology, and laboratory, imaging, or anatomopathological confirmation were not considered in the analysis due to a lack of registered data on this basis. Moreover, this is a retrospective observational cohort study, which inherently carries limitations in reviewing patient records. Nonetheless, periodic audits were conducted to ensure data quality.

On the other hand, as a study strength, the utilization of advanced PSM techniques enhances the robustness of our findings by minimizing selection bias and confounding effects, thus providing a more accurate estimation of the impact of cirrhosis on COVID-19 outcomes. This methodological rigor underscores the validity and reliability of our study's conclusions, contributing valuable insights to the existing body of knowledge. Furthermore, our study features an expressive number of patients across 41 different hospitals. The geographical diversity

of hospitals across various regions of Brazil guarantees a diverse representation of the population in the study. Additionally, we analyzed data from the pre and post-vaccination phases. Most studies involving patients with cirrhosis were only developed in the first phase of the pandemic, with non-vaccinated patients.

Conclusion

This study includes 41 hospitals from the Northeast to the South of Brazil, representing a diverse cross-section of the large Brazilian population. We found that Brazilian COVID-19 inpatients with cirrhosis had significantly higher in-hospital mortality rates, and higher frequencies of ICU admission, IMV, dialysis, and other severe outcomes, as well as higher frequency of institution of palliative care when compared to the control group. Our findings underscore the need for these patients to receive particular attention from healthcare teams and allocated resources.

Abbreviations

ACLF	Acute-on-chronic liver failure
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CAAE	*Certificado de Apresentação para Apreciação Ética*-Certificate of Presentation for Ethical Assessment
CAD	Coronary artery disease
CKD	Chronic kidney disease
CONEP	*Comissão Nacional de Ética em Pesquisa*-Brazilian National Research Ethics Committee
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 19
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IgM	Immunoglobulin M
IMV	Invasive mechanical ventilation
INR	International normalized ratio
IQR	Interquartile ranges
MELD	Model for End-stage Liver Disease
REDCap®	Research Electronic Data Capture
RR	Relative risk
RT-PCR	Real-time polymerase chain reaction
S1	Supplementary 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VTE	Venous thromboembolism

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10424-x.

Supplementary Material 1

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Author contributions

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by CONEP (Comissão Nacional de Ética em Pesquisa - National Research Ethics Committee - Certificate of Presentation for Ethical Assessment 30350820.5.1001.0008). Individual informed consent was waived by Comissão Nacional de Ética em Pesquisa - National Research Ethics Committee due to the pandemic situation and the use of data from medical records. This study had internal approval of ethics boards from each hospital. The study adhered to the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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