Research Article
Cirrhosis and Liver Failure

JOURNAL
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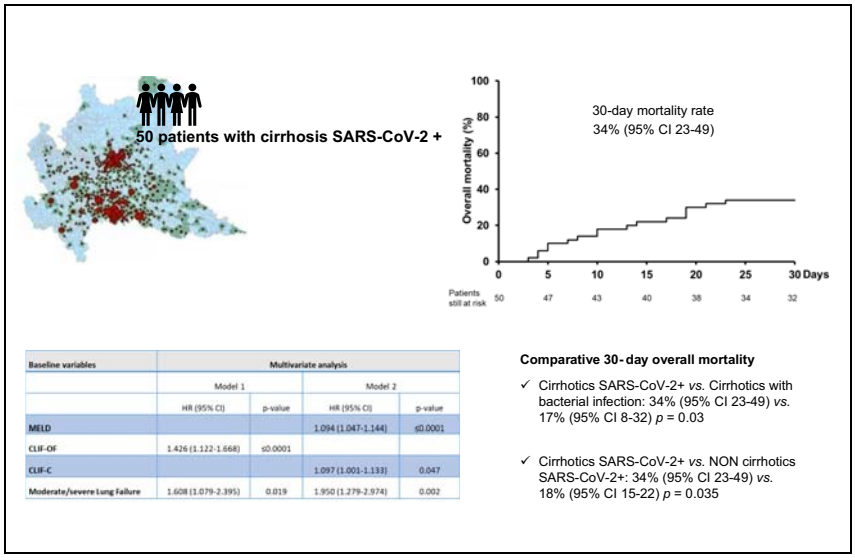
# High rates of 30-day mortality in patients with cirrhosis and COVID-19

## Graphical abstract




| Baseline variables | Multivariate analysis | | | |
|---|---|---|---|---|
| | Model 1 | | Model 2 | |
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| MELD | | | 1.094 (1.047-1.144) | ≤0.0001 |
| CLIF-OF | 1.426 (1.122-1.668) | ≤0.0001 | | |
| CLIF-C | | | 1.097 (1.001-1.133) | 0.047 |
| Moderate/severe Lung Failure | 1.608 (1.079-2.395) | 0.019 | 1.950 (1.279-2.974) | 0.002 |

## Highlights

- 50 patients with cirrhosis and SARS-CoV-2 infection were studied, with an overall 30-day mortality rate of 34%.
- Mortality was higher in patients with respiratory failure and in those with worsening liver function at COVID-19 diagnosis.
- 30-day mortality rates were higher in patients with cirrhosis and COVID-19 than in those with bacterial infections.
- No major adverse events were related to the thromboprophylaxis with heparin (given to 80% of patients) or antiviral treatments.

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## Lay summary

Coronavirus disease 2019 (COVID-19) poses a major health threat to healthy individuals and those with comorbidities. Herein, we assessed its impact on patients with cirrhosis. Infection with COVID-19 was associated with liver function deterioration and elevated mortality in patients with cirrhosis.

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# High rates of 30-day mortality in patients with cirrhosis and COVID-19

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**Background & Aims:** Coronavirus disease 2019 (COVID-19) poses a major health threat to healthy individuals and those with comorbidities, but its impact on patients with cirrhosis is currently unknown. Herein, we aimed to evaluate the impact of COVID-19 on the clinical outcome of patients with cirrhosis.

**Methods:** In this multicentre retrospective study, patients with cirrhosis and a confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection were enrolled between 1st and 31th March 2020. Clinical and biochemical data at diagnosis of COVID-19 and at the last outpatient visit were obtained through review of medical records.

**Results:** Fifty patients with cirrhosis and confirmed SARS-CoV-2 infection were enrolled (age 67 years, 70% men, 38% virus-related, 52% previously compensated cirrhosis). At diagnosis, 64% of patients presented fever, 42% shortness of breath/polypnea, 22% encephalopathy, 96% needed hospitalization or a prolonged stay if already in hospital. Respiratory support was necessary in 71%, 52% received antivirals, 80% heparin. Serum albumin significantly decreased, while bilirubin, creatinine and prothrombin time significantly increased at COVID-19 diagnosis compared to last available data. The proportion of patients with a model for end-stage liver disease (MELD) score ≥15 increased from 13% to 26% ($p = 0.037$), acute-on-chronic liver failure and *de novo* acute liver injury occurred in 14 (28%) and 10 patients, respectively. Seventeen patients died after a median of 10 (4–13) days from COVID-19 diagnosis, with a 30-day-mortality rate of 34%. The severity of lung and liver (according to CLIF-C, CLIF-OF and MELD scores) diseases independently predicted mortality. In patients with cirrhosis, mortality was significantly higher in those with COVID-19 than in those hospitalized for bacterial infections.

**Conclusion:** COVID-19 is associated with liver function deterioration and elevated mortality in patients with cirrhosis.

**Lay summary:** Coronavirus disease 2019 (COVID-19) poses a major health threat to healthy individuals and those with comorbidities. Herein, we assessed its impact on patients with cirrhosis. Infection with COVID-19 was associated with liver function deterioration and elevated mortality in patients with cirrhosis.



## Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus first detected in Wuhan, China, that causes coronavirus disease 2019 (COVID-19).[1] Since the initial detection of the virus, more than 1,350,000 cases of COVID-19 have been confirmed worldwide, with the first reported cases in the Lombardy region, Northern Italy, occurring in late February, 2020.[2] The number of cases in our region continued to rise; as of April 2, 2020, there had been 46,071 confirmed SARS-CoV-2 infections and 7,600 deaths.[3]

At least 7 relatively large-scale case studies from China have reported the clinical features of patients with COVID-19.[4–10] These data indicate that 2–11% of patients with COVID-19 had pre-existing liver diseases. Recently, Grasselli *et al.*, reported that, among the first 1,591 patients admitted to intensive care units

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(ICUs) in Lombardy due to SARS-CoV-2 infection, 3% had a history of chronic liver disease.[11] Patients with pre-existing cirrhosis might be more susceptible to SARS-CoV-2 infection because of their systemic immunocompromised status. Moreover, in these patients, the severity of COVID-19 and the rate of complications, potentially leading to increased liver-related mortality, might be more pronounced than in the general population. This hypothesis derives from studies on bacterial infections, a common cause of decompensation in patients with cirrhosis; conversely, data on the impact of viral infections have been less well studied in this population.[12] It has been reported that viral influenza may increase the risk of decompensation in patients with cirrhosis, and recently it was reported that even patients with stable liver disease were at a high risk of hepatic function deterioration during the H1N1 influenza virus pandemic of 2009.[13] In the study by Premkumar *et al.*, 82% of patients with cirrhosis and A/H1N1/09 died of pneumonia and acute respiratory distress syndrome despite timely antiviral treatment, with the severity of both respiratory distress and kidney impairment being independent predictors of mortality.[13]

Since data on COVID-19 in patients with cirrhosis are lacking, we performed a multicentre retrospective study to describe the demographic, clinical and biochemical characteristics of patients with cirrhosis and SARS-CoV-2 infection in the Lombardy region and their outcomes.

## Patients and methods

### Study population

We included patients with cirrhosis and laboratory-confirmed SARS-CoV-2 infection who were managed in 9 hospitals in Lombardy, Northern Italy, between March 1$^{st}$ and March 31$^{th}$, 2020. Therefore, all information registered by 3 April 2020 (data-lock) were entered into the database.

A confirmed case of SARS-CoV-2 was defined by a positive result on a reverse-transcription PCR (RT-PCR) assay of a specimen collected on a nasopharyngeal swab, as previously described.[5] Demographic and clinical data, including clinical symptoms or signs at presentation, laboratory and radiologic results during COVID-19 management as well as administered antiviral therapies and anti-thrombotic prophylaxis, were collected. All laboratory tests and radiologic assessments were performed at the discretion of the treating physician. Data from the last outpatient clinic visit before COVID-19 were also collected for comparison. When SARS-CoV-2 infection occurred during hospitalization, data at COVID-19 diagnosis were compared to those collected at hospital admission.

The Steering Committee for the COVID-19 studies at Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico approved the study, which was notified to the Ethical Committee of Milan Area 2. The protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki.

### Data collection

Liver function was evaluated by means of both biochemical (*i.e.* bilirubin, international normalized ratio [INR], albumin, creatinine) and clinical variables (*i.e.* occurrence of ascites, encephalopathy, bleeding disorders). For each patient, Child-Pugh, model for end-stage liver disease (MELD), CLIF-OF and CLIF-C (European Foundation for the study of chronic liver failure organ failure and cirrhosis) scores were assessed. Liver injury was defined as alanine aminotransferase (ALT) level >30 U/L for males and 19 U/L for females in those patients with normal ALT levels at last outpatient visit.[14] Hepatic flare was defined as ALT level ≥5 × the upper limit of normal. Acute-on-chronic liver failure (ACLF) at diagnosis of COVID-19 was retrospectively defined and graded according to the EASL-CLIF definition.[15]

Any coexisting conditions were obtained from medical records. Scrutiny for other causes of liver function deterioration included history of over the counter medication use, overdiuresis, alcohol intake and use of hepatotoxic medications.

### Comparative analyses

To assess the impact of SARS-CoV-2 infection on survival of hospitalized patients with cirrhosis, we compared the survival of this cohort with that of a control group which included patients hospitalized in the last year for liver decompensation due to bacterial infection in 2 units involved in this multicentre study. These control patients, identified from the discharge database, were consecutively selected among those diagnosed with cirrhosis and infection (*i.e.* pneumonia, urinary tract infection, spontaneous bacterial peritonitis, or spontaneous bacteraemia); all of their data was retrieved from hospital records.

To compare the mortality of patients with COVID-19, with and without cirrhosis, we retrospectively extracted the mortality rates due to COVID-19 in patients without cirrhosis hospitalized at the Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico within the same period. Finally, SARS-CoV-2-related mortality data for the general population were retrieved from the regional report of the Italian Istituto Superiore di Sanità (ISS), and used as benchmark.

### Statistical analysis

Descriptive statistics were used to summarize the data; results have been reported as median (IQR) or mean (SD), as appropriate. Categorical variables have been compared using the $\chi^2$ or the Fisher's exact tests; continuous variables have been compared using the Student's *t* test, the Mann-Whitney *U* test or the Kruskall-Wallis test, when appropriate. All tests were 2-sided and used a significance level of 0.05. Survival curves were estimated by the Kaplan-Meier method, Cox regression analysis was used to identify factors associated with 30-day mortality. Data handling and analysis were performed using STATA software (release 7.0, Stata Corporation, College Station, TX).

## Results

### Demographic and clinical characteristics of the patients

Between March 1$^{st}$ and March 31$^{th}$, 50 patients with cirrhosis and confirmed SARS-CoV-2 infection were identified. All of the patients were on regular hepatologic follow-up for their liver disease at the time of SARS-CoV-2 diagnosis.

The demographic and clinical characteristics of the patients are reported in Table 1. The median age was 67 (61–74) years, 70% were men, 28% had HCV-related and 10% had HBV-related cirrhosis; all patients with virus-related cirrhosis were either HCV-RNA negative after anti-HCV treatment or on long-term anti-HBV treatment. Among our patients, there were only 3 with metabolic (*i.e.* non-alcoholic fatty liver disease [NAFLD]/non-alcoholic steatohepatitis [NASH]) aetiology. Diabetes was present in 18 (36%) and arterial hypertension in 29 (58%) patients. Twenty-six (52%) patients had compensated cirrhosis (Child-Pugh A) at the time of their last outpatient visit. Seven (14%) were on the waiting list for liver transplantation (LT).

**Table 1. Demographic and clinical characteristics of the 50 patients with cirrhosis enrolled in the study.**

| Characteristics | Patients (n = 50) |
|---|---|
| Age, years | 67 (61-74) |
| Males | 35 (70) |
| Aetiology of liver disease | |
| HCV* | 14 (28) |
| HBV* | 5 (10) |
| Alcohol | 12 (24) |
| Other aetiologies** | 9 (18) |
| Multiple aetiologies | 10 (20) |
| Oesophageal varices | 28 (56) |
| Active or previous HCC | 11 (22) |
| Enlisted for liver transplantation | 7 (14) |
| Comorbidities: | |
| Diabetes | 18 (36) |
| Arterial hypertension | 29 (58) |
| Obesity | 8 (16) |
| Chronic kidney disease | 8 (16) |
| Chronic obstructive pulmonary disease | 8 (16) |
| Current or former tobacco smoker | 20 (40) |
| Suspected route of SARS-CoV-2 infection | |
| Community-acquired | 30 (60) |
| Healthcare-related | 20 (40) |

Values are reported as n (%) or median (IQR).
*All patients with HCV achieved a sustained virological response and all patients with HBV were on effective nucleotide analogue therapy. **Other aetiologies: autoimmune hepatitis/cholangitis (n = 3); non-alcoholic steatohepatitis (n = 3); erythropoietic protoporphyria (n = 1); unknown (n = 2). HCC, hepatocellular carcinoma; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Median time from last outpatient visit was 1.7 (1.0–4.0) months. SARS-CoV-2 infection was community acquired in 30 (60%) patients and healthcare related in the remaining 20 (40%). In fact, 10 (50%) patients reported a history of recent (less than 7 days) hospitalization or admission to hospital services, whilst the other 10 (50%) probably got infected during current hospitalization.

At SARS-CoV-2 diagnosis, 44 (88%) patients presented at least 1 symptom: 18 (36%) presented with cough, 21 (42%) with polypnea or shortness of breath, 32 (64%) with fever and 11 (22%) with acute hepatic encephalopathy (Table 2). Six (12%) patients were asymptomatic at presentation: in these cases, nasopharyngeal swab was performed according to surveillance protocols (*i.e.* contact with positive individuals).

Finally, 48 (96%) patients were hospitalized, which included 10 patients already hospitalized for other reasons and 38 who required admission for SARS-CoV-2 infection itself.

## COVID-19 outcome

Thirty-two (64%) patients needed non-invasive respiratory support during hospitalization, while 2 patients were admitted to ICU and received invasive mechanical ventilation (Table 2). In detail, an acute respiratory distress syndrome was present in 26 (52%) patients: mild (200 mmHg< $PaO_2/FiO_2$ ≤300 mmHg) in 12, moderate (100 mmHg< $PaO_2/FiO_2$ ≤200 mmHg) in 11 and severe ($PaO_2/FiO_2$ <100 mmHg) in 3 patients. Moreover, 4 (8%) patients experienced hypotension and needed vasopressors.

Overall, 26 (52%) patients received specific anti-SARS-CoV-2 treatment: 9 (18%) received hydroxychloroquine alone, 3 (6%) received antiviral therapy with lopinavir–ritonavir, and 14 (28%) received both antiviral treatment and hydroxychloroquine; none of the patients have been treated with tocilizumab or remdesivir. Only mild gastrointestinal adverse events were reported in patients treated with hydroxychloroquine, whilst 1 patient showed a mild increase in ALT values. In 1 case, treated with hydroxychloroquine plus lopinavir–ritonavir, a prolongation of electrocardiographic QT interval occurred, leading to treatment discontinuation, without sequelae.

Thromboprophylaxis with heparin (mainly with low molecular weight heparin [LMWH]) was started at COVID-19 diagnosis

**Table 2. Presentation of SARS-CoV-2 infection in 50 cirrhotic patients enrolled in the study.**

| Characteristics | Patients (n = 50) |
|---|---|
| Respiratory symptoms | |
| Cough | 18 (36) |
| Shortness of breath/polypnea | 21 (42) |
| Systemic signs and symptoms | |
| Fever | 32 (64) |
| Fatigue | 30 (60) |
| Acute hepatic encephalopathy | 11 (22) |
| Myalgia/arthralgia | 10 (20) |
| Diarrhoea | 5 (10) |
| Acute kidney impairment | 2 (4) |
| Headache | 1 (2) |
| $PaO_2/FiO_2$, mmHg | |
| >400 | 14 (28) |
| >300-≤400 | 10 (20) |
| >200-≤300 | 12 (24) |
| >100-≤200 | 11 (22) |
| ≤100 | 3 (6) |
| Suggestive features of COVID-19 pneumonia at imaging | |
| Chest radiography | 22/37 (59) |
| Chest computed tomography | 24/35 (69) |
| Blood tests | |
| Hepatitic flares§ | 6 (12) |
| Lactate dehydrogenase, U/L* | 323 (267–408) |
| D-dimer, mg/L* | 1,850 (1,092–4,232) |
| C-reactive protein, mg/dl | 5 (3–15) |
| Ferritin, ng/ml | 800 (404–1,567) |
| Grades of ACLF# | |
| No ACLF | 36 (72) |
| ACLF Ia | 3 (6) |
| ACLF Ib | 5 (10) |
| ACLF II | 5 (10) |
| ACLF III | 1 (2) |
| CLIF-OF score | 7 (4–9) |
| CLIF-C ACLF score | 64 (61–67) |
| Hospitalization status | |
| Hospitalized for SARS-CoV-2 | 38 (76) |
| Already hospitalized for different reasons | 10 (20) |
| Outpatient clinic management | 2 (4) |
| Respiratory support | |
| High-flow nasal cannula | 12 (24) |
| CPAP or non-invasive positive pressure | 20 (40) |
| Invasive mechanical ventilation | 2 (4) |
| None | 16 (32) |
| Treatments | |
| None | 24 (48) |
| Hydroxychloroquine | 9 (18) |
| Lopinavir/ritonavir | 3 (6) |
| Hydroxychloroquine and lopinavir/ritonavir | 14 (28) |

Values are reported as n (%) or median (IQR).
#according to the EASL-CLIF classification and grades of ACLF; *Chest radiography: *i.e.* bilateral infiltrates and pleural effusion; Chest computed tomography: *i.e.* bilateral ground-glass opacification, nodules, pleural effusion; §Hepatitic flares: alanine aminotransferase ≥5× the upper limit of normal. ACLF, acute-on-chronic liver failure; CLIF, European Foundation for the study of chronic liver failure; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; EASL, European Association for the Study of the Liver; $FiO_2$, fraction of inspired oxygen; OF, organ failure; $PaO_2$, partial pressure of arterial oxygen; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

in 80% of patients, with 2 minor haemorrhagic events (epistaxis and haematuria). Progression of pre-existing portal thrombosis was ascertained in 1 patient, despite LMWH use. Patients in thromboprophylaxis *vs.* those untreated were comparable in terms of INR (1.23 [1.09–1.55] *vs.* 1.45 [1.21–1.54]; $p = 0.97$) and platelet count (132,000 [85,000-183,000] *vs.* 89,000 [34,500-136,000] per microliter, $p = 0.064$), more frequently had well-compensated cirrhosis (Child-Pugh A in 51% *vs.* 18%, $p = 0.05$), and less frequently oesophageal varices (42% *vs.* 81%, $p = 0.023$).

At data-lock (April, 30), among the 48 hospitalized patients, 17 (35%) died during hospital stay, 24 (50%) were discharged home after recovery (median length of stay 15 [10–23] days), and 7 (15%) were still hospitalized (median length of stay at data-lock 15 [9–33] days).

## COVID-19 impact on cirrhosis

When compared to the last outpatient visit (median time-lapse 1.7 [1.0–4.0] months), or to blood tests performed at admission, but before SARS-CoV-2 infection, most parameters had changed at the time of COVID-19 diagnosis. Bilirubin, INR, ALT and creatinine ($p = 0.007$) significantly increased ($p = 0.026$, $p = 0.042$, and $p = 0.024$, respectively), whilst albumin levels significantly decreased ($p = 0.0003$), thus influencing both Child-Pugh and MELD scores (Table 3). The distribution of Child-Pugh scores significantly changed ($p = 0.05$, Table 3), the number of patients with MELD ≥15 increased from 5 to 13 (13% *vs.* 26%, $p = 0.037$) and 12 out of 26 (46%) patients decompensated. No upper-gastrointestinal bleeding episodes occurred, despite the wide use of anti-thrombosis prophylaxis. ACLF at COVID-19 was diagnosed in 14 (28%) patients: Ia in 3, Ib in 5, II in 5 and III in 1.

Acute liver injury occurred in 10 (45%) of 22 patients with previously persistent normal ALT levels, while 6 (12%) patients experienced a hepatitis flare. All other causes of acute liver injury had been ruled out, in all patients.

## Overall and disease-specific mortality

Seventeen (34%) patients died after a median of 10 (4–13) days from diagnosis of SARS-CoV-2 infection, and their median age was 70 (61–80) years. COVID-19 with respiratory failure was considered the cause of death in 12 (71%) patients, while end-stage-liver disease (ESLD) accounted for death in 5 (29%). Nevertheless, all patients dying of ESLD required respiratory support for concomitant hypoxemic respiratory failure. Three (18%) of the 17 patients who died were on the LT waiting list.

The 30-day cumulative probability of overall mortality was 34% (95% CI 23–49) (Fig. 1A). The corresponding features for COVID-19- and liver-related mortality were 25% (95% CI 15–40) and 12% (95% CI 5–26), respectively (Fig. 1B). Predictors of mortality are reported in Table 4. In the multivariate analysis, only CLIF-OF (HR 1.426; 95% CI 1.122–1.668; $p \leq 0.0001$) and moderate/severe lung failure (HR 1.608; 95% CI 1.079–2.395; $p = 0.019$) independently predicted mortality. When CLIF-C ACLF score was introduced, MELD, CLIF-C ACLF score and moderate/severe respiratory failure remained as independent predictors. MELD and CLIF also independently predicted mortality when analysed as dichotomous variables. Fig. 2A,B show the cumulative probability of mortality according to MELD ≥15 and CLIF-OF >9 at

**Table 3. Comparison of clinical and biochemical characteristics of cirrhotic patients at last visit* and at SARS-CoV-2 diagnosis.**

| Variables | Before COVID-19° | At COVID-19 diagnosis | *p* value |
|---|---|---|---|
| Albumin, g/dl | 3.4 (3.2–3.9) | 2.8 (2.6–3.2) | 0.0003 |
| Bilirubin, mg/dl | 1.3 (0.8–2.8) | 1.8 (0.8–3.8) | 0.026 |
| INR | 1.2 (1.1–1.6) | 1.3 (1.1–1.7) | 0.042 |
| Ascites | 17 (34) | 19 (38) | 0.621 |
| Encephalopathy | 9 (18) | 19 (38) | 0.025 |
| PLT | | | |
| count/mm$^3$ | 115,000 (76,500–159,250) | 111,500 (61,000–171,750) | 0.197 |
| ≤50,000/mm$^3$ | 7/44 (16) | 11 (22) | 0.425 |
| WBC | | | |
| count/mm$^3$ | 4,500 (3,973–6,510) | 5,680 (4,100–8,370) | 0.559 |
| ≥10,000/mm$^3$ | 6/44 (14) | 10/49 (20) | 0.387 |
| ≤4,000/mm$^3$ | 11/44 (25) | 11/49 (22) | 0.773 |
| Lymphocyte | | | |
| count/mm$^3$ | 1,157 (955–1,573) | 995 (638–1,380) | 0.067 |
| ≤1,500/mm$^3$ | 23/34 (68) | 37/48 (77) | 0.342 |
| AST | | | |
| U/L | 33 (25–68) | 48 (35–87) | 0.176 |
| >40 U/L | 15/43 (35) | 32/48 (67) | 0.002 |
| ALT | | | |
| U/L | 31 (24–51) | 54 (24–85) | 0.024 |
| >40 U/L | 18/45 (40) | 29 (58) | 0.003 |
| Creatinine, mg/dl | 1.0 (0.8–1.3) | 1.1 (0.8–1.6) | 0.007 |
| Child-Pugh score: | | | 0.05 |
| A (5-6) | 26 (52) | 20 (40) | |
| B (7-9) | 18 (36) | 14 (28) | |
| C (10-15) | 6 (12) | 16 (33) | |
| MELD score | 6 (6–9) | 9 (6–15) | 0.0003 |
| MELD score ≥15 | 5 (10) | 13 (26) | 0.037 |

Values are reported as n (%) or median (IQR). Categorical variables have been compared using the $\chi^2$ test, continuous variables have been compared using the Student's *t* test, all tests were 2-sided and used a significance level of 0.05.

*At last outpatient visit or at hospital admission (if SARS-CoV-2 diagnosed during hospitalization). °Last available outpatient visit or inpatients data before SARS-CoV-2 infection. ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; INR, international normalized ratio; MELD, model for end-stage liver disease; PLT, platelets; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WBC, white blood cell.

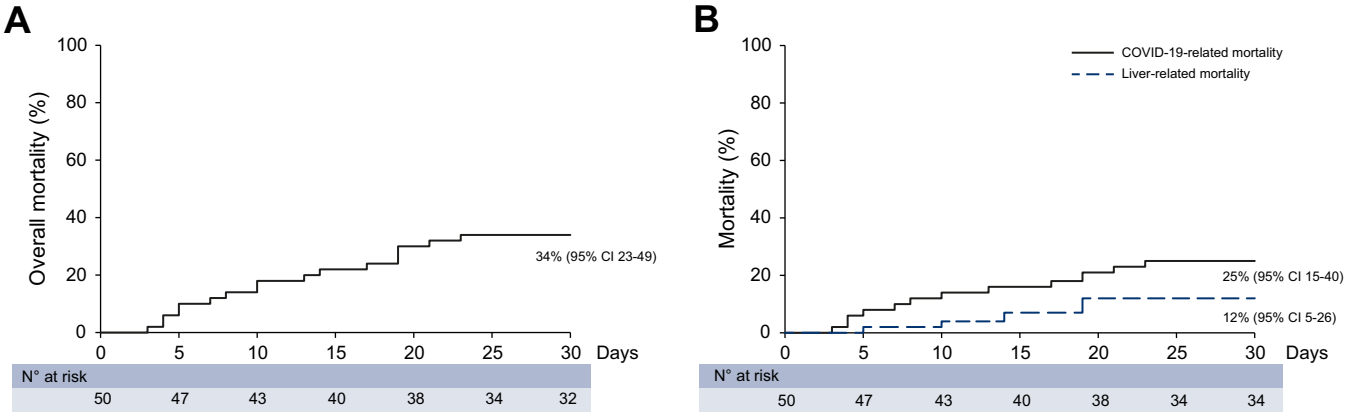


**Fig. 1. 30-day cumulative probability of overall mortality and COVID-19-related or liver-related mortality.** (A) 30-day cumulative probability of overall mortality and (B) 30-day cumulative probability of either COVID-19-related or liver-related mortality; survival curves were estimated by the Kaplan-Meier method.

**Table 4. Predictors of 30-day mortality in 50 cirrhotic patients at COVID-19 diagnosis.**

| | Univariate analysis[$] | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|
| | | | Model 1[§] | | Model 2[#] | |
| **Baseline variables** | **HR (95% CI)** | ***p* value** | **HR (95% CI)** | ***p* value** | **HR (95% CI)** | ***p* value** |
| Creatinine, mg/dl | 1.803 (1.172–2.775) | 0.007 | | | | |
| Child-Pugh score A | 0.275 (0.0788–0.958) | 0.043 | | | | |
| MELD | 1.067 (1.027–1.109) | 0.001 | | | 1.094 (1.047–1.144) | ≤0.0001 |
| MELD ≥15 | 5.183 (1.975–13.600) | 0.001 | | | | |
| Delta-MELD* | 5.689 (2.093–15.460) | 0.001 | | | | |
| CLIF-OF | 1.396 (1.204–1.618) | ≤0.0001 | 1.426 (1.122–1.668) | ≤0.0001 | | |
| CLIF-OF >9 | 9.386 (3.349–26.302) | ≤0.0001 | | | | |
| CLIF-C ACLF | 1.145 (1.050–1.248) | 0.002 | | | 1.097 (1.001–1.133) | 0.047 |
| CLIF-C ACLF ≥70 | 5.078 (1.916–13.459) | 0.001 | | | | |
| Moderate/severe lung failure** | 2.928 (1.124–7.627) | 0.028 | 1.608 (1.079–2.395) | 0.019 | 1.950 (1.279–2.974) | 0.002 |

Cox regression analysis was used to identify factors associated with 30-day mortality and used a significance level of 0.05.
ACLF, acute-on-chronic liver failure; CLIF, European Foundation for the study of chronic liver failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HR, hazard ratio; MELD, model end-stage liver disease; OF, organ failure.
[$]Other variables included in the univariate analysis did not result significantly associated to 30-day mortality: age, sex, aetiology of liver disease, diabetes mellitus, smoking history, HCC history, bilirubin level, albumin level, ferritin level, LDH level.
*variation >5 points between last MELD before COVID-19 diagnosis and diagnosis of COVID-19; **PaO2/FiO2 ≤200 mmHg.
[§]Model 1: MELD, delta-MELD, CLIF-OF and moderate/severe respiratory failure.
[#]Model 2: MELD, delta-MELD, CLIF-C ACLF and moderate/severe respiratory failure.

diagnosis. MELD ≥15 at development of SARS-CoV-2 infection occurred in 2/33 (6%), 5/10 (50%) and 6/7 (86%) of patients with MELD scores of 6, 7–11 and >11 at last record before SARS-CoV-2 infection, respectively ($p$ <0.0001).

### Comparative analysis

Table 5 shows the comparison between the main cohort (*i.e.* 48 patients with cirrhosis hospitalized with COVID-19) and 47 patients with cirrhosis hospitalized for acute liver decompensation due to bacterial infection, which served as controls. In the control group, bacterial pneumonia was diagnosed in 18 (38%) patients, spontaneous bacteraemia in 14 (30%), cholangitis in 5 (11%), urinary tract infection in 4 (9%), spontaneous bacterial peritonitis in 4 (9%) patients, arthritis in 1 (2%) and gastroenteritis due to *Clostridioides difficile* in 1 (2%). Patients with COVID-19 were significantly older, with lower white blood cells counts despite concomitant infection, and lower MELD and Child-Pugh scores. However, ACLF prevalence was similar (Table 5). The 30-day cumulative probability of overall mortality was 17% (95% CI 8–32) *vs.* 34% (95% CI 23–49; $p$ = 0.03). At multivariate analysis, COVID-19 (HR 3.594; 95% CI 1.465–8.819; $p$ = 0.005) and CLIF-OF (HR 1.369; 95% CI 1.219–1.539; $p$ ≤0.0001) independently predicted mortality.

During the study period, 399 patients without cirrhosis required hospitalization at the Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico (Milan), following COVID-19 diagnosis: median age was 62 (51–76) years, 256 (64%) were males. Eighty-one (20%) of these patients died (median age at death 80 [75–86] years). In patients with COVID-19, 30-day mortality was lower in those without cirrhosis than in those with cirrhosis (18% [95% CI 15–22] *vs.* 34% [95% CI 23–49], $p$ = 0.035).

## Discussion

This case series clearly demonstrates that patients with cirrhosis (either with compensated or decompensated liver disease) who develop COVID-19 have poor outcomes. The main causes of death were respiratory complications but also the sudden worsening of liver function leading to ESLD. To the best of our

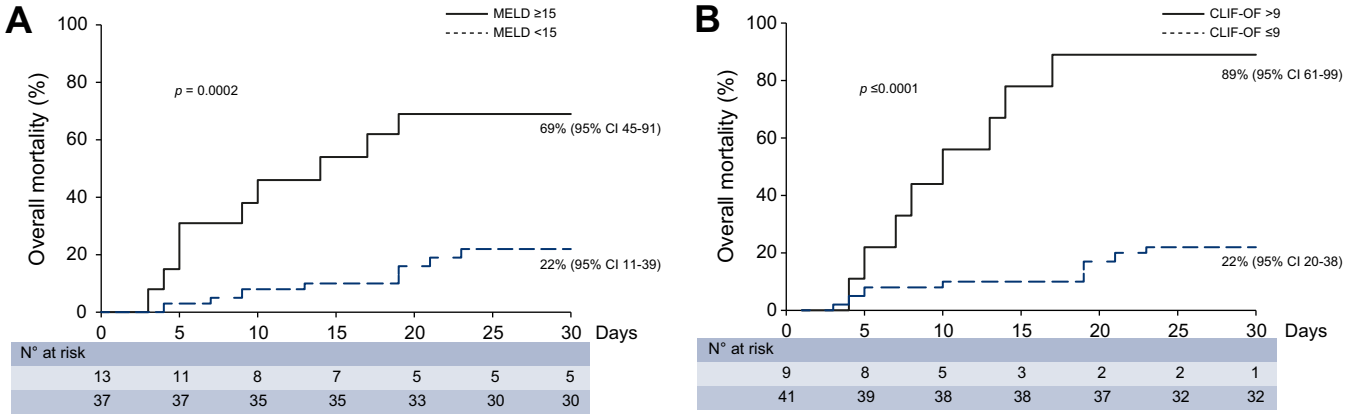


**Fig. 2. 30-day cumulative probability of overall mortality according to liver function at COVID-19 diagnosis.** 30-day cumulative probability of overall mortality according to (A) MELD ≥15 status at COVID-19 diagnosis and (B) CLIF-OF >9 status at COVID-19 diagnosis; survival curves were estimated by the Kaplan-Meier method with a significance level of $p \leq 0.05$.

knowledge, this is the first report on the clinical impact of SARS-CoV-2 infection in patients with cirrhosis.

We retrospectively collected data on 50 patients with known cirrhosis and COVID-19 managed in 9 hospitals in Lombardy. Interestingly, a healthcare-related SARS-CoV-2 infection was registered in 40% of our patients. This fact could be the consequence of their general increased need for hospitalization and assistance due to cirrhosis complications, as well as their increased susceptibility to infections. According to the Italian ISS report, the nosocomial SARS-CoV-2 infection rate was 9.9% in Italy, which is lower than we observed in our cohort. Moreover, the clinical presentation of SARS-CoV-2 infection in our cohort slightly differed from that reported in the general population. Indeed, fever was less frequent,[16] whilst an expected increase in cirrhosis complications rate was observed, particularly hepatic encephalopathy. In our study, the 30-day mortality rate was higher in patients with moderate/severe respiratory failure and in those who had worse liver function, as indicated by the increased MELD and CLIF-OF scores at COVID-19 diagnosis. While the association between severity of lung failure and early mortality was expected, this study is the first to define the predictive role of CLIF and MELD scores in the setting of acute failure of chronic liver disease due to COVID-19.

The corresponding 30-day mortality rate in non-cirrhotic patients hospitalized following a COVID-19 diagnosis was significantly lower, with higher median age of deceased patients. Unfortunately, no data are available on the role of factors (*i.e.* comorbidities, lung failure severity, *etc.*) potentially influencing mortality rates in this control group, as the ICD-9 system has been used for data collection. In the same period, 7,600 (16%) of 46,071 patients with SARS-CoV-2 infection died in Lombardy, at a median age of 79 years (73–87). These data differ significantly from what we reported in our cirrhotic cohort, which was characterized by a higher mortality rate and lower age at death.

Moreover, our study highlighted that infection with SARS-CoV-2 led to rapid clinical deterioration in otherwise stable cirrhotic patients: 25 Child-Pugh A patients with low MELD score experienced a rapid deterioration in their liver function, so that Child-Pugh score increased to B/C after COVID-19 diagnosis in more than a third of them. This was even worst for those patients with decompensated disease before SARS-CoV-2 infection, since we reported that high MELD scores at last visit independently predicted the risk of MELD ≥15 at COVID-19 diagnosis. The short interval between the last outpatient visit (or hospital admission) before SARS-CoV-2 diagnosis, supports the role of this acute infection in worsening liver function, which is common in patients with cirrhosis of any aetiology. The comparative analysis of patients with cirrhosis hospitalized for decompensation due to bacterial infections confirmed that the mortality rate due to infections is high, irrespective of the etiological agent. However, in patients with cirrhosis, 30-day mortality was higher in those infected with COVID-19 than in those hospitalized following bacterial infections, despite the MELD score being lower in the former group. Multivariate analysis confirmed that COVID-19, together with high CLIF-OF, was independently associated with 30-day mortality. This is probably due to several factors, which include the unavailability of effective treatments against SARS-CoV-2 as well as the impact of lung failure on early mortality even in patients who died because of ESLD. In fact, in patients who died of ESLD, respiratory function had been severely compromised by SARS-CoV-2, since all of them needed respiratory support.

Several papers reported on the impact of SARS-CoV-2 infection on transaminase levels in the general population, although they did not specifically focus on the clinical significance of these alterations in terms of both morbidity and mortality, especially in patients with cirrhosis.[17,18] In the setting of chronic liver diseases, persistent and/or severe alterations of transaminases may negatively impact on the course of cirrhosis, even in patients who had remained stable and free from liver complications for a long time. Recently, Dong *et al.* reported a 50% ALT increase in 202 consecutive patients with confirmed COVID-19, which included 38% with NAFLD. Interestingly, the authors reported that patients with NAFLD had a higher likelihood of abnormal liver function tests from admission to discharge (70% [53/76] *vs.* 11.1% [14/126], $p$ <0.0001).[18] Our study is the first reporting on the impact of SARS-CoV-2 infection on ALT levels in patients with cirrhosis, showing that acute liver injury was observed in nearly 50% of patients with previously normal transaminases values. Moreover, a hepatitis flare was not uncommon at SARS-CoV-2 diagnosis. However, more data are needed to clarify the impact of an ALT increase on the natural history of patients with

**Table 5. Clinical and biochemical characteristics of the cirrhotic patients hospitalized with COVID-19 (n = 48) and with bacterial infection (n = 47).**

| Characteristics | Cirrhotic patients SARS-CoV-2 positive (n = 48) | Cirrhotic patients SARS-CoV-2 negative (n = 47) | *p* value |
|---|---|---|---|
| Age, years | 67 (61–73) | 59 (50–65) | 0.0009 |
| Males | 33 (69) | 35 (74) | 0.54 |
| Liver disease aetiology: | | | 0.07 |
| HCV* | 14 (29) | 7 (15) | |
| HBV* | 4 (8) | 0 | |
| Alcohol | 12 (25) | 18 (38) | |
| Other aetiologies** | 5 (10) | 13 (28) | |
| Multiple aetiologies | 10 (21) | 9 (19) | |
| HCC*** | 13 (27) | 11 (23) | 0.68 |
| Enlisted for LT | 7 (15) | 7 (15) | 0.93 |
| Comorbidities: | | | |
| Diabetes | 18 (38) | 11 (23) | 0.16 |
| Obesity | 8 (17) | 7 (15) | 0.87 |
| Arterial hypertension | 29 (60) | 14 (30) | 0.003 |
| Chronic kidney disease | 8 (17) | 4 (9) | 0.15 |
| COPD | 8 (17) | 5 (11) | 0.41 |
| Blood tests: | | | |
| Lactate dehydrogenase, U/L* | 325 (267–432) | 233 (172–283) | 0.005 |
| CRP, mg/dl | 4.7 (2.3–15.9) | 4.75 (2.9–8.3) | 0.70 |
| Bilirubin, mg/dl | 1.9 (0.8–3.8) | 5.6 (1.8–14.4) | 0.09 |
| Albumin, g/dl | 2.8 (2.6–3.2) | 2.9 (2.6–3.2) | 0.97 |
| INR | 1.30 (1.12–1.70) | 1.54 (1.31–1.85) | 0.34 |
| PLT $\times 10^3/mm^3$ | 112 (63–171) | 77 (42–175) | 0.45 |
| WBC $\times 10^3/mm^3$ | 5,73 (4.25–8.65) | 8.31 (5.65–12.92) | 0.01 |
| ALT, U/L | 54 (24–88) | 44 (29–84) | 0.87 |
| Creatinine, mg/dl | 1.1 (0.80–1.62) | 1.0 (0.7–1.4) | 0.77 |
| Ascites | 18 (38) | 29 (62) | 0.014 |
| Encephalopathy | 19 (40) | 24 (51) | 0.23 |
| Child-Pugh score: | | | |
| A (5-6) | 18 (38) | 4 (9) | 0.004 |
| B (7-9) | 14 (29) | 20 (42) | |
| C (10-15) | 16 (33) | 23 (49) | |
| MELD score: | | | |
| Median | 9 (6–16) | 19 (14–25) | <0.0001 |
| ≥15 | 13 (27) | 32 (68) | <0.0001 |
| Grades of ACLF#: | | | |
| No ACLF | 34 (71) | 30 (64) | 0.77 |
| ACLF Ia | 3 (6) | 2 (4) | |
| ACLF Ib | 5 (10.5) | 7 (15) | |
| ACLF II | 5 (10.5) | 5 (11) | |
| ACLF III | 1 (2) | 3 (6) | |
| CLIF-OF score | 7 (4–9) | 7 (4–9) | 0.92 |
| CLIF-C ACLF score | 64 (61–67) | 61 (57–66) | 0.27 |

Values are reported as n (%) or median (IQR). Categorical variables have been compared using the $\chi^2$ test, continuous variables have been compared using the Student's *t* test, all tests were 2-sided and used a significance level of 0.05.

ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; CLIF, European Foundation for the study of chronic liver failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C reactive protein; HCC, hepatocellular carcinoma; INR, international normalized ratio; LT, liver transplant; MELD, model end-stage liver disease; NASH, non-alcoholic steatohepatitis; OF, organ failure; PLT, platelets; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

*All patients with HCV achieved an sustained virological response and all patients with HBV were on effective nucleotide analogue therapy; **11 autoimmune hepatitis and 8 NASH in the SARS-CoV-2 negative cohort; ***active or past; #according to the EASL-CLIF classification and grades of ACLF.

cirrhosis and SARS-CoV-2 infection, and to better explain the pathogenic mechanism of coronavirus in causing liver damage at the level of liver cells. A potential direct cytopathic effect has been suggested, since the abundant angiotensin-converting enzyme 2 receptors in the liver might favour SARS-CoV-2 entry into the hepatocytes.[19] Otherwise, the liver might be indirectly involved in the severe inflammatory response following SARS-CoV-2 infection, as it contains a large number of macrophages (Kupffer cells) and is a potent cytokine producer.[20]

Specific treatment against SARS-CoV-2 was not standardized in our cohort, but rather based upon regional guidelines issued by scientific societies and expert opinions. For each patient, physicians had to make decisions based on the balance between rapidly available repurposed drugs and acceptable tolerability and safety. Most patients received hydroxychloroquine, while only one-third received lopinavir/ritonavir. With all the caveats of a small sample size, only 1 major adverse event was reported (QT prolongation leading to drug discontinuation). Generally, lopinavir/ritonavir has been used cautiously in patients with more advanced cirrhosis, due to its known hepatic metabolism and its possible detrimental effect on residual hepatic function. At the time of data collection, a phase II trial with tocilizumab was available in only a few referral centres, thus excluding the chance to enrol patients with cirrhosis. In the period before data-lock, access to remdesivir was reserved for mechanically ventilated patients on the basis of a treating physician-initiated request in a compassionate use program. The 2 intubated patients in our cohort did not receive remdesivir. The reasons for

not applying for compassionate use in these 2 cases are unknown but could be due to the dramatic hospital emergency we faced in March 2020 in Lombardy.

Interestingly, most patients (80%) in our cohort received thromboprophylaxis, mainly with LMWH, without any evidence of major haemorrhagic complications. The high prevalence of thromboprophylaxis in our cohort might be explained by the established awareness of the increased thrombotic risk in this population, as well as by the ascertained skill in anti-thrombotic management in most centres managing patients with cirrhosis.

We are aware that our study suffers from some limitations, mainly due to the retrospective design of the study. They include the limited number of patients, the short follow-up following the diagnosis of SARS-CoV-2 infection and the low number of patients admitted to ICUs. However, we believe that this last point might not only be a consequence of the retrospective collection of data but also of the effective limited access to ICUs of patients with severe comorbidities, such as cirrhosis. In fact, during the study period, we were faced with a dramatic scarcity of ICU beds in Italy. Another limitation is the imbalance of baseline characteristics (age and MELD) between patients with viral and bacterial infection, although multivariate analysis confirmed SARS-CoV-2 infection as an independent predictor of 30-day mortality. On the other hand, the strengths of our study include the involvement of most tertiary referral centres for both infectious and liver diseases in Lombardy, thus limiting the risk of underestimating the number of hospitalized patients with cirrhosis within our region, as well as the availability of "historical" information for almost all patients. The inclusion of control groups of well characterized hospitalized patients with cirrhosis and acute decompensation following bacterial infection, and without cirrhosis but with COVID-19, further strengthens the present study.

In conclusion, as the current pandemic of SARS-CoV-2 is spreading, physicians and hepatologists should be aware of the potential detrimental effects of this infection on short-term outcomes in fragile patient populations, such as those with cirrhosis.

### Abbreviations

ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; CLIF, European Foundation for the study of chronic liver failure; COVID-19, coronavirus disease 2019; ESLD, end-stage liver disease; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; LMWH, low molecular weight heparin; LT, liver transplantation; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OF, organ failure; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

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## Conflict of interest

Massimo Iavarone: Speaking/Teaching, consultant and advisory board for Bayer, Gilead Sciences, BMS, Janssen, Ipsen, MSD, BTG-Boston Scientific, AbbVie, Guerbet, EISAI; Roberta D'Ambrosio: teaching and speaking for AbbVie, Gilead, MSD; Advisory Board for AbbVie, MSD, Research Grant from Gilead; Alessandro Soria: Speaking/Teaching, consultant and advisory board for AbbVie, MSD, Gilead; Mauro Viganò: speaking and teaching for Fujirebio, Intercept, Gilead; Alessio Aghemo: Advisory Board/Speaker Bureau for: Gilead, AbbVie, Intercept, MSD, Mylan and Alfasigma, Research grants from Gilead and Abbvie; Stefano Fagiuoli: Advisory Board/Speaker Bureau for Gilead, AbbVie, Novartis, MSD, Bayer, Intercept, Kedrion; Pietro Invernizzi: Advisory Board/Speaker Bureau for Gilead, Intercept, Bruschettini, AbbVie, MSD; Pietro Lampertico: Advisory Board/Speaker Bureau for BMS, Roche, Gilead, GSK, AbbVie, MSD, Arrowhead, Alnylam, Janssen, Spring Bank, MYR, Eiger. The other authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

Concept and design: Massimo Iavarone and Alessandro Soria; data collection: Roberta D'Ambrosio, Alessandro Soria, Michela Triolo, Nicola Pugliese, Paolo Del Poggio, Giovanni Perricone, Angiola Spinetti, Elisabetta Buscarini, Sara Massironi, Mauro Vigano, Stefano Fagiuoli, Alessio Aghemo, Luca S. Belli, Canio Carriero, Marianna Pedaci, Martina Lucà, Alessandro Rimondi; statistical analysis: Massimo Iavarone, Pietro Lampertico; writing of the article: Massimo Iavarone, Roberta D'Ambrosio, Alessandro Soria and Pietro Lampertico; Critical revision of the manuscript: Mauro Vigano, Alessio Aghemo, Maria Grazia Rumi, Pietro Invernizzi, Paolo Bonfanti and Luca S. Belli.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.06.001.

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*Author names in bold designate shared co-first authorship*

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