Original research

# COVID-19 in liver transplant candidates: pretransplant and post-transplant outcomes - an ELITA/ELTR multicentre cohort study

Luca Saverio Belli ,[1] Christophe Duvoux,[2] Paolo Angelo Cortesi ,[3] Rita Facchetti,[3] Speranta Iacob,[4] Giovanni Perricone ,[5] Sylvie Radenne,[6] Sara Conti,[7] Damiano Patrono,[8] Gabriela Berlakovich,[9] Angus Hann,[10] Luisa Pasulo,[11] Lluis Castells,[12] Francois Faitot,[13] Olivier Detry,[14] Federica Invernizzi,[15] Giulia Magini,[16] Paolo De Simone,[17] Ilias Kounis ,[18] Maria Cristina Morelli,[19] Fernando Díaz Fontenla ,[20] Bo-Göran Ericzon,[21] Carmelo Loinaz,[22] Chris Johnston,[23] Liliana Gheorghe,[24] Mickael Lesurtel,[25] Renato Romagnoli ,[8] Dagmar Kollmann,[9] M Thamara PR Perera,[26] Stefano Fagiuoli,[27] Darius Mirza,[26] Audrey Coilly,[28,29] Christian Toso,[30] Krzysztof Zieniewicz,[31] Laure Elkrief,[32] Vincent Karam,[33] Rene Adam,[33] Caroline den Hoed,[34] Marco Merli,[35] Massimo Puoti,[35] Luciano De Carlis,[36] Gabriel C Oniscu,[21] Salvatore Piano,[37] Paolo Angeli ,[37] Constantino Fondevila,[38] Wojciech G Polak,[39] for all the centres contributing to the ELITA-ELTR COVID-19 Registry

## ABSTRACT

**Objective** Explore the impact of COVID-19 on patients on the waiting list for liver transplantation (LT) and on their post-LT course.

**Design** Data from consecutive adult LT candidates with COVID-19 were collected across Europe in a dedicated registry and were analysed.

**Results** From 21 February to 20 November 2020, 136 adult cases with laboratory-confirmed SARS-CoV-2 infection from 33 centres in 11 European countries were collected, with 113 having COVID-19. Thirty-seven (37/113, 32.7%) patients died after a median of 18 (10–30) days, with respiratory failure being the major cause (33/37, 89.2%). The 60-day mortality risk did not significantly change between first (35.3%, 95% CI 23.9% to 50.0%) and second (26.0%, 95% CI 16.2% to 40.2%) waves. Multivariable Cox regression analysis showed Laboratory Model for End-stage Liver Disease (Lab-MELD) score of ≥15 (Model for End-stage Liver Disease (MELD) score 15–19, HR 5.46, 95% CI 1.81 to 16.50; MELD score≥20, HR 5.24, 95% CI 1.77 to 15.55) and dyspnoea on presentation (HR 3.89, 95% CI 2.02 to 7.51) being the two negative independent factors for mortality. Twenty-six patients underwent an LT after a median time of 78.5 (IQR 44–102) days, and 25 (96%) were alive after a median follow-up of 118 days (IQR 31–170).

**Conclusions** Increased mortality in LT candidates with COVID-19 (32.7%), reaching 45% in those with decompensated cirrhosis (DC) and Lab-MELD score of ≥15, was observed, with no significant difference between first and second waves of the pandemic. Respiratory failure was the major cause of death. The dismal prognosis of patients with DC supports the adoption of strict preventative measures and the urgent testing of vaccination efficacy in this population. Prior SARS-CoV-2 symptomatic infection did not affect early post-transplant survival (96%).

## INTRODUCTION

Patients with cirrhosis are at increased risk of infections and associated complications due to cirrhosis-associated immune dysfunction,[1–4] with bacterial infections being the most frequent trigger of acute decompensation (AD) and acute-on-chronic liver failure (ACLF).[5 6] Existing evidence indicates the possibility that viral infections may cause AD and ACLF.[7] Although data on the role of SARS-CoV-2 are limited, SARS-CoV-2 is particularly feared for patients with decompensated cirrhosis (DC) on the waiting list (WL) for liver transplantation (LT), as ACLF may lead to early death if patients cannot be transplanted in due time.[8] Furthermore, the impact of SARS-CoV-2 infection on patients being transplanted after recovering from SARS-CoV-2 is relatively unknown. Thus, the European Liver and Intestine Association (ELITA) and the European Liver Transplant Registry (ELTR) called for a prospective registry aiming to address the following issues:

1. What is the mortality risk of COVID-19 in LT candidates and which are the determinants of death on clinical presentation?
2. How frequently does COVID-19 trigger ACLF, thus increasing the urgency for LT after recovering from COVID-19? Conversely, how many

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2021-324879).

For numbered affiliations see end of article.

**Correspondence to**
Dr Luca Saverio Belli, Hepatology and Gastroenterology, ASST Grande Ospedale Metropolitano Niguarda, Milano, MI 20162, Italy;
luca.belli@ospedaleniguarda.it

LSB, CD and PAC are joint first authors.
CF and WGP are joint senior authors.

Received 9 April 2021
Accepted 24 June 2021
Published Online First 19 July 2021

Check for updates



**To cite:** Belli LS, Duvoux C, Cortesi PA, *et al*. *Gut* 2021;**70**:1914–1924.

## Significance of this study

**What is already known on this subject?**

- Many publications have explored the impact of COVID-19 on patients with chronic liver disease, but no study has focused on patients on the waitlist for liver transplantation (LT).

**What are the new findings?**

- LT candidates with COVID-19 were at high risk of early death (32.7%), reaching 49.2% in those with decompensated cirrhosis (DC) and Laboratory Model for End-stage Liver Disease (Lab-MELD) score of ≥15, which is triple the mortality risk observed in listed patients with comparable Lab-MELD scores without COVID-19.
- The evaluation of two simple variables, Model for End-stage Liver Disease (MELD) class of ≥15 or <15 and dyspnoea (present or absent), allowed a clear distinction between the individual mortality risks on clinical presentation.
- Respiratory failure frequently resulted in LT candidate ineligibility for LT and was the most frequent cause of death.
- During the two waves of the pandemic, clinical presentation, course and mortality risk of COVID-19 did not significantly change.
- Short-term survival after LT was 96%, and no cases of SARS-CoV-2 reinfection were observed to date.

**How might it impact on clinical practice in the foreseeable future?**

- LT candidates with DC should rigorously adopt all the usual measures to prevent SARS-CoV-2 infection and reinforced vaccination programmes should be implemented as the efficacy of standard vaccines is much lower than that reported in the registration studies.
- The evaluation of lab-MELD score and dyspnoea at clinical presentation will aid clinicians in their decision-making.
- LT in patients with prior COVID-19 is encouraged.

patients developed severe respiratory failure and were removed from the WL?

3. What is the post-LT course of patients with pre-LT COVID-19?
4. Did clinical presentation and course of COVID-19 differ between the two waves of the pandemic?

## METHODS

### Study population

ELITA/ELTR COVID-19 registry was circulated in February 2020 among 149 LT centres affiliated to ELTR and located in 30 European countries. All centres reporting at least one case were provided with a database and instructions on how to record structured data. Thirty-three centres responded having observed SARS-CoV-2 infection in adult LT candidates from 21 February to 20 November 2020.

Inclusion criteria include adult patients listed for LT, patients presenting with symptoms consistent with SARS-CoV-2 infection and confirmation of SARS-CoV-2 infection by a positive result on a reverse-transcriptase PCR (RT-PCR) assay of a specimen collected on a nasopharyngeal swab or on bronchoalveolar lavage.

Exclusion criteria include patients with RT-PCR-confirmed SARS-CoV-2 infection without symptoms.

### Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

### Data collection and definitions

Demographic and clinical data, including clinical symptoms or signs on presentation, laboratory and radiological results during COVID-19 management, administered antiviral therapies and antithrombotic prophylaxis were retrospectively collected. All laboratory tests and radiological assessments were performed on the discretion of the treating physician. Serum creatinine was converted to milligram per decilitre for analysis. Obesity was defined as a Body Mass Index of >30 kg/m$^2$. Model for End-stage Liver Disease (MELD) score stands for pure Laboratory Model for End-stage Liver Disease (Lab-MELD) score without additional points. Dyspnoea at admission was considered when combined with $O_2$ saturation below 95. AD was defined as including one or more among the following events: de novo or worsening ascites, new or worsening hepatic encephalopathy, bacterial infection and/or variceal haemorrhage. The EASL Chronic Liver Failure Consortium (CLIF-C) definitions were used to determine the presence of ACLF in patients with AD and to calculate the CLIF-C-OF score and the CLIF-C ACLF score.[8] The submitted files from each centre were manually reviewed to assess for data quality, completeness and inconsistencies. In addition, submitting clinicians were contacted and asked to provide corrections or data integration whenever needed.

### Comparative analysis

To understand the relative impact of COVID-19 on survival of cirrhotic patients listed for LT, a comparison was made with a control group of 91 cirrhotic patients hospitalised in 2016–2020 for AD triggered by bacterial infection. This control group was also used to evaluate the impact of COVID-19 on liver function deterioration related to ACLF development and associated mortality.

### Regulatory approval

Data were collected in accordance with General Data Protection Regulation, the European Union legislation and the ELTR privacy policy.

### Statistical analysis

Analysis was led by the Research Centre on Public Health, University of Milan-Bicocca, Monza, Italy. A descriptive analysis of the cohort was carried out on the overall population and following stratification of the population by site of management, at home, in general wards and in intensive care units (ICU). Categorical variables were summarised through percentages, and continuous variables through median, first quartile and third quartile. Categorical variables were compared using the $\chi^2$ or Fisher's exact test; continuous variables were compared using the Mann-Whitney U-test or the Kruskall-Wallis test, when appropriate. All tests were two-sided and used a significance level of 0.05.

Cumulative incidence curves for LT from WL were constructed considering death as a competing risk.[9] The association between mortality and baseline clinically relevant characteristics of symptomatic patients were evaluated through univariate Cox proportional hazard models. All characteristics analysed in the univariate model were included in a stepwise selection process that identified the best multivariate model.

To compare the effect of COVID-19 or bacterial infection on risk of death, Cox proportional hazard models were performed after adjusting for MELD or Child-Pugh, and age, sex, aetiology and diabetes mellitus.

A further analysis was conducted to compare the patient characteristics and outcomes of LT candidates infected during the two waves of the pandemic. The end of the first wave (June 2020) and the beginning of the second wave (July 2020) were identified analysing the graphical trend in the number of new patients with COVID-19 reported in the registry. Overall survival of all patients was also provided. All statistical analyses were conducted using SAS V.9.4 and R V.4.0.0 (R Core Team, Vienna, Austria). The map was drawn using QGIS software V.3.10 (QGIS Development Team).

## RESULTS

### LT candidates with SARS-CoV-2 infection: patient disposition

Thirty-three centres from 11 European countries observed at least one LT candidate with RT-PCR-confirmed SARS-CoV-2 infection. Of the 1865 patients on the WL at the participating sites, 136 LT candidates with SARS-CoV-2 infection (7.29%) were consecutively reported in the registry. Twenty-three (16.9%) were asymptomatic at the time of diagnosis, with the RT-PCR test being performed due to surveillance protocols for being in contact with a SARS-CoV-2-positive subject (13 cases), for screening at the time of LT (8 cases) and for screening at hospital admission for cirrhosis complications (2 cases). On comparing the baseline characteristics of the two groups of symptomatic and asymptomatic cases, no major significant differences emerged between the two populations (online supplemental table 1). These 23 asymptomatic cases were excluded for the analysis and their outcome is reported in online supplemental figure 1. The remaining 113 subjects (113/136, 83.1%), representing the 6.05% of the subjects on the WL, presented with symptomatic SARS-CoV-2 infection (COVID-19) and were analysed (figure 1 and online supplemental figure 2).

### Characteristics and clinical course of 113 patients with COVID-19

Thirty-three patients (29.2%) received homecare, and the remaining 80 patients (70.8%) required hospitalisation (figure 1), with 52 (65%) patients being treated in a general ward and 28 (35%) in the ICU. Baseline patient characteristics are reported in table 1. The median age was 58.0 (IQR 53–63) and 61.9% were men. DC with or without hepatocellular carcinoma (HCC) (68.1%) and HCC on compensated cirrhosis (17.7%) were the main indications for LT.

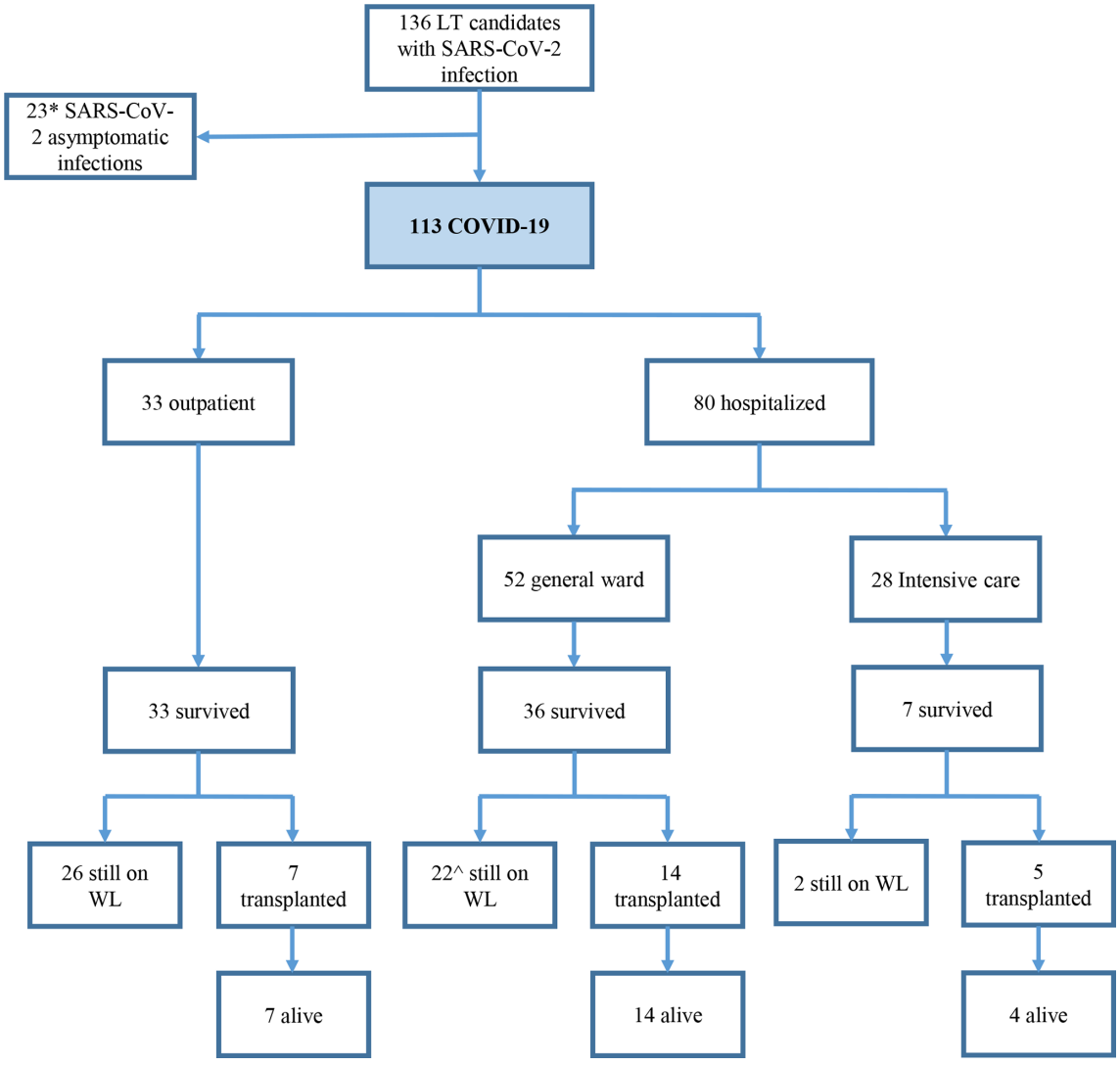


**Figure 1** Flowchart showing the selection of the study population and intermediate/final outcomes. LT, liver transplantation; WL, waiting list.

**Table 1** Baseline characteristics of the COVID-19 cases

| | Total (N=113) |
|---|---|
| Male, n (%) | 70 (61.9) |
| Age at symptoms (years) | |
| Median (IQR) | 58 (53–63) |
| Age class at symptoms (years), n(%) | |
| ≤50 | 23 (20.4) |
| 50–60 | 43 (38.1) |
| >60 | 47 (41.6) |
| Location of patient at occurrence of symptoms, n(%) | |
| Home | 75 (67) |
| Hospital | 35 (31.3) |
| On arrival for LT | 2 (1.8) |
| Missing | 1 |
| Indication for LT, n (%) | |
| Decompensated cirrhosis with or without HCC* | 77 (68.1) |
| HCC | 20 (17.7) |
| Other† | 16 (14.2) |
| Aetiology, n (%) | |
| Alcohol | 30 (26.5) |
| Alcohol+NASH | 8 (7.1) |
| Alcohol+HCV active or inactive | 5 (4.4) |
| AIH+PBC+PSC | 17 (15) |
| HBV | 12 (10.6) |
| HCV active or inactive | 9 (8) |
| NASH | 8 (7.1) |
| Other | 24 (21.2) |
| Comorbidities,N(%) | |
| No | 29 (25.7) |
| Diabetes mellitus | 45 (39.8) |
| Arterial hypertension | 26 (23) |
| BMI>30 kg/m$^2$ | 23 (20.4) |
| Current or former tobacco smoker | 18 (15.9) |
| Kidney function impairment‡ | 12 (10.6) |
| Chronic obstructive lung disease | 5 (4.4) |
| Coronary artery disease | 4 (3.5) |
| Other | 6 (5.3) |
| Number of comorbidities class, n (%) | |
| 0 | 29 (25.7) |
| 1 | 46 (40.7) |
| 2 | 24 (21.2) |
| ≥3 | 14 (12.4) |
| Drugs, n (%) | |
| No | 63 (55.8) |
| Beta blockers | 37 (32.7) |
| ACE inhibitors or angiotensin II receptor antagonists | 7 (6.2) |
| Beta blockers+ACE inhibitors | 6 (5.3) |
| MELD score pre-COVID-19, n (%) | |
| Median (IQR) | 16 (11–21) |
| <15 | 42 (37.2) |
| 15–19 | 34 (30.1) |
| ≥20 | 37 (32.7) |
| Child-Pugh score pre-COVID-19,§ n (%) | |
| Median (IQR) | 8 (7–10) |
| 5–6 | 25 (23.6) |
| 7–9 | 42 (39.6) |
| ≥10 | 39 (36.8) |
| Missing | 1 |
| International Norm INR pre-COVID-19 | |
| Median (IQR) | 1.4 (1.2–1.8) |
| Bilirubin (mg/dL) pre-COVID-19 | |
| Median (IQR) | 2.7 (1–8) |
| Creatinine (mg/dL) pre-COVID-19 | |
| Median (IQR) | 0.9 (0.8–1.3) |
| Ascites pre-COVID-19,§ n (%) | |
| 0=no | 34 (32.7) |
| 1=only at ultrasound | 17 (16.3) |
| 2=moderate | 32 (30.8) |
| 3=severe or tense ascites | 6 (5.8) |
| 4=refractory | 15 (14.4) |
| Missing | 3 |
| Hepatic encephalopathy pre-COVID-19,§ n (%) | |
| 1=absent | 81 (77.9) |
| 2=grades 1–2 | 21 (20.2) |
| 3=grades 3–4 | 2 (1.9) |
| Missing | 3 |

Pre-COVID-19 denotes most recent value before symptoms.
*72 of 77 patients without HCC and 5 of 77 with HCC.
†Re-LT for chronic rejection or hepatic artery thrombosis; autosomal dominant polycystic liver disease; neuroendocrine tumour; primary sclerosing cholangitis; surgical biliary complication.
‡P-creatinine >2 mg/dL
§6 patients without cirrhosis were excluded.
AIH, autoimmune hepatitis; BMI, Body Mass Index; HCC, hepatocellular carcinoma; INR, international normalised ratio; LT, liver transplant; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

## Comorbidities

Forty-five (39.8%) patients had diabetes mellitus; 26 (23.2%) had arterial hypertension; 12 (10.7%) had renal function impairment with serum creatinine of >2 mg/dL; and 5 (4.5%) had chronic obstructive lung diseases. Eighty-four (74.3%) patients had at least one comorbidity and 38 (33.6%) patients had two or more (table 1).

## Clinical presentation and course

At diagnosis, the most common symptoms included fever (74 patients, 65.5%), cough (64 patients, 56.6%) and dyspnoea (30 patients, 26.6%). Radiological imaging (CT scan or chest X-ray) showed typical ground-glass opacities in 61 cases (54%) (table 2), with bacterial pneumonia being superimposed in one-third of the cases (20/61=32.7%).

Overall, 56 (49.6%) patients required respiratory support during hospitalisation, with 13 requiring non-invasive ventilation and 15 requiring,invasive mechanical ventilation. Forty-nine patients received specific anti-SARS-CoV-2 treatment based on local protocols. Twenty-nine patients (25.7%) were treated with low-molecular weight heparin. Two patients experienced pulmonary thromboembolism; neither was on heparin prophylaxis.

## Clinical features and outcomes in patients treated at home, in general wards and in the ICU

Baseline characteristics and disease course of patients with less severe symptoms who could be treated at home and of those with more severe symptoms requiring hospitalisation in general wards and in ICU are reported in online supplemental table 2 and 3. Patients treated at home had lower Child-Pugh and

**Table 2** Clinical presentation and course after COVID-19 symptoms

| | Total (N=113) |
|---|---|
| Symptoms at clinical diagnosis, n(%) | |
| Fever>37.2°C | 74 (65.5) |
| Cough | 64 (56.6) |
| Dyspnoea | 30 (26.6) |
| Fatigue | 19 (16.8) |
| Confusion | 14 (12.4) |
| Diarrhoea | 13 (11.5) |
| Muscle pain | 9 (8) |
| Thoracic pain | 5 (4.4) |
| Anosmia and dysgeusia | 4 (3.5) |
| Other | 4 (3.5) |
| Chest X-ray or thorax CT scan, n(%) | |
| No | 12 (10.7) |
| Yes, normal | 39 (34.8) |
| Yes, ground-glass opacities | 58 (51.8%) |
| Yes, lobar infiltrates+ground-glass opacities | 3 (2.7) |
| Missing | 1 |
| Respiratory support, n(%) | |
| No | 57 (50.4) |
| $O_2$ support | 28 (24.8) |
| Non-invasive ventilation | 13 (11.5) |
| Invasive mechanical ventilation | 15 (13.3) |
| AD, n (%) | |
| No | 75 (66.4) |
| Yes | 34 (30.1) |
| Yes, unrelated to COVID-19 | 4 (3.5) |
| ACLF, n (%) | |
| No ACLF | 93 (82.3) |
| ACLF grade 1a | 0 (0) |
| ACLF grade 1b | 2 (1.8) |
| ACLF grade 2 | 3 (2.7) |
| ACLF grade 3a | 3 (2.7) |
| Unrelated to COVID-19 | 1 of 3 |
| ACLF grade 3b | 12 (10.6) |
| Unrelated to COVID-19 | 2 of 12 |
| CLIF-C ACLF score | |
| Median (IQR) | 60.82 (11–42) |
| Renal replacement therapy, n (%) | 9 (8) |
| Vasoactive drugs (norepinephrine), n (%) | 16 (14.3) |
| Myocarditis, n (%) | 3 (2.7) |
| Bilirubin (mg/dL): peak value | |
| Median (IQR) | 3.2 (1.4–10.1) |
| INR: peak value | |
| Median (IQR) | 1.5 (1.2–2) |
| Creatinine (mg/dL): peak value | |
| Median (IQR) | 1.1 (0.8–1.6) |
| MELD score: peak value | |
| Median (IQR) | 18 (13–25) |
| COVID-19 therapy, n (%) | |
| None | 64 (56.6) |
| Low-molecular weight heparin | 29 (25.7) |
| OH-chloroquine | 16 (14.2 |
| Azythromicin | 14 (12.4) |
| High-dose steroids | 7 (6.2) |
| Lopinavir/ritonavir | 5 (4.4) |
| Tocilizumab | 5 (4.4) |
| Remdesevir | 4 (3.5) |
| Other | 2 (1.8) |
| Outcome, n (%) | |
| Alive | 75 (66.4%) |
| Dead | 37 (32.7%) |
| Death after LT | 1 (0.9%) |
| Time between symptoms and last follow-up (days) | |
| Median (IQR) | 55 (27–183) |
| Cause of death, N (%) | |
| Respiratory failure | 10 (27) |
| Liver failure+respiratory failure | 20 (54.1) |
| Liver failure without respiratory failure | 4 (10.8) |
| Other causes+respiratory failure | 3 (8.1) |
| Patients having received an LT, n (%) | 26 (23) |
| Time between symptoms and LT (days), median (IQR) | 78.5 (44–102) |

ACLF, acute-on-chronic liver failure; AD, acute decompensation; CLIF-C, Chronic Liver Failure Consortium; LT, liver transplantation; MELD, Model for End-stage Liver Disease.

biochemical MELD scores, while age and number of comorbidities were similar.

### Wait-list mortality and predictive factors

Thirty-seven patients died (37/113, 32.7%) after a median of 18 (IQR 10–30) days from diagnosis, the great majority (33/37, 89.1%) with respiratory failure. The remaining four patients died of end-stage liver disease without respiratory failure after 18, 67, 205 and 210 days from COVID-19 diagnosis with only two of them being SARS-CoV-2 negative. The cumulative incidence of death and LT by competitive risk analysis is reported in online supplemental figure 3. On clinical presentation, the following five factors were significantly associated with mortality risk by univariable analysis: DC with or without HCC, dyspnoea, kidney function impairment with serum creatinine of >2 mg/dL, Lab-MELD class of 15–19 and Lab-MELD class of ≥20 (table 3). Estimated probability of survival stratified by main indication for LT (DC, HCC and other indications), Lab-MELD score on presentation (<15, 15–20 and >20), dyspnoea on presentation and kidney function impairment are shown in figure 2A–D. Three factors resulted significantly associated to mortality in multivariable analysis, namely, dyspnoea (HR 3.89, 95% CI 2.02 to 7.51), MELD class of 15–19 (HR 5.46, 95% CI 1.81 to 16.50) and MELD class of ≥20 (HR 5.24, 95% CI 1.77 to 15.55). The Kaplan-Meier survival curves stratified by MELD class of ≥15 or <15 and dyspnoea (present or absent) allowed a clear distinction between the individual mortality risks on clinical presentation (figure 3). Kaplan-Meier (KM) survival of the whole population and after stratification by place of management, defined as the place of highest intensity of care during COVID-19 (at home, in general ward or in ICU), is provided in online supplemental figure 4. All patients managed at home survived, while the probability of survival at 30 days was 80.8% (95% CI 67.2% to 89.2%) and 35.7% (95% CI 18.9% to 53.0%) for patients treated in the general ward and in the ICU, respectively, and this declined to 69.7% (95% CI 53.5% to 81.2%) and 24.5% (95% CI 10.6% to 41.5%) at 90 days.

**Table 3** Results from univariate and multivariate analyses of baseline predictors of mortality, from Cox proportional hazard regression models

| | Univariable models | | Multivariable model | |
|---|---|---|---|---|
| **Variable** | **HR (95% CI)** | **P value** | **HR (95% CI)** | **P value** |
| Age (years) | | | | |
| <50 | 1 ref | | | |
| 50–64 | 1.028 (0.435 to 2.432) | 0.95 | | |
| ≥65 | 1.827 (0.694 to 4.808) | 0.22 | | |
| Gender, male versus female | 1.072 (0.551 to 2.084) | 0.84 | | |
| Indication for LT | | | | |
| HCC | 1 ref | | | |
| Decompensated cirrhosis without HCC | **10.567 (1.444 to 77.327)** | **0.020** | | |
| Other | 4.126 (0.429 to 39.682) | 0.22 | | |
| Aetiology | | | | |
| HBV, HCV or other cirrhosis | 1 ref | | | |
| Alcohol | 1.354 (0.677 to 2.709) | 0.39 | | |
| NASH | 1.195 (0.348 to 4.107) | 0.78 | | |
| Other non-cirrohsis | 1.095 (0.251 to 4.776) | 0.90 | | |
| Dyspnoea as presenting symptom | **4.087 (2.139 to 7.808)** | **<0.001** | **3.894 (2.018 to 7.514)** | **<0.0001** |
| BMI≥30 vs BMI<30 | 0.860 (0.378 to 1.960) | 0.72 | | |
| Diabetes mellitus (yes vs no) | 1.426 (0.748 to 2.717) | 0.28 | | |
| Kidney function impairment with p-creatinine>2 mg/dL | **2.61 (1.142 to 5.972)** | **0.023** | | |
| Number of comorbidities | | | | |
| 0 | 1 ref | | | |
| 1 | 0.689 (0.298 to 1.595) | 0.38 | | |
| 2 | 0.831 (0.316 to 2.19) | 0.71 | | |
| 3+ | 2.071 (0.813 to 5.271) | 0.13 | | |
| MELD class | | | | |
| MELD<15 | 1 ref | | 1 ref | |
| MELD 15–19 | **5.267 (1.746 to 15.888)** | **0.003** | **5.463 (1.808 to 16.5016)** | **0.003** |
| MELD≥20 | **6.055 (2.048 to 17.906)** | **0.001** | **5.242 (1.768 to 15.545)** | **0.003** |

BMI, Body Mass Index; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, Model for End-stage Liver Disease; ref, reference.

### Impact of COVID-19 on liver function deterioration: AD and ACLF

A total of 38 patients (38/113=33.6%) presented or developed AD during COVID-19. Decompensation events included new or worsening ascites of 55.3% (21/38), hepatic encephalopathy of 57.9% (22/38), spontaneous bacterial peritonitis of 31.6% (12/38) and variceal haemorrhage of 13.2% (5/38). Twenty of these 38 patients with AD (55.2%) met the criteria for ACLF: grade 1b in 2, grade 2 in 3, grade 3a in 3 and grade 3b in 12, with mortality being significantly higher in patients with ACLF compared with no ACLF (85% vs 21.7%, p<0.001) (table 2).

### Comparative analysis: ACLF induced by COVID-19 or by bacterial infection

Online supplemental table 4 shows the comparison between cirrhotic patients with COVID-19 listed for LT (n=106 of 113 patients) and cirrhotic patients hospitalised for AD due to bacterial infection (n=91) serving as the control group. The two cohorts were similar for gender distribution and MELD/Child-Pugh scores, whereas patients with COVID-19 were significantly younger and their liver disease was less frequently caused by alcohol use disorders. The 30-day cumulative probability of overall mortality was similar, 24.8% (95% CI 17.6% to 34.2%) vs 28.5% (95% CI 20.2% to 39.3%, p=0.50), and did not vary across different MELD (<15, 15–19 and ≥20) and Child-Pugh classes, adjusted for possible confounders (online supplemental figure 5). ACLF incidence resulted lower in patients with COVID-19 (18.9% vs 30.8%), although mortality after developing ACLF was significantly higher for patients having ACLF triggered by COVID-19 (85% vs 53%), which is explained by the frequent occurrence of refractory respiratory failure in patients with COVID-19 and ACLF (18/20 vs 0/28).

### Comparative analysis: first and second waves

Fifty-one patients developed COVID-19 between February and June 2020 (first wave), and 62 between July and November 2020 (second wave) (online supplemental figure 6). Clinical presentation and course were similar between the two waves, the only difference being a twofold increase in the percentage of patients receiving heparin during the second wave. The 60-day mortality risk in the overall population was 35.3% (95% CI 23.9% to 50.0%) vs 26.0% (95% CI 16.2% to 40.2%), and peaked to 43.9% (95% CI 30.4% to 60.3%) vs 41.7% (95% CI 26.6% to 61.0%) in those requiring hospitalisation, with respiratory failure being the major cause of death (table 4 and online supplemental figure 7).

### Outcome of LT in patients with prior COVID-19

Twenty-six patients underwent an LT after a median interval of 78.5 (IQR 44–102) days from diagnosis (table 2). Before being reactivated on the WL, all patients had to be asymptomatic and with a minimum of one negative RT-PCR rhinopharyngeal swab. An additional negative swab at the time of LT was required by all centres. Overall, the median ICU and hospital stay were 3 (IQR 3–6) and 11 (IQR 8–19) days, respectively. Immunosuppression included a calcineurin inhibitor drug in all patients (24 tacrolimus

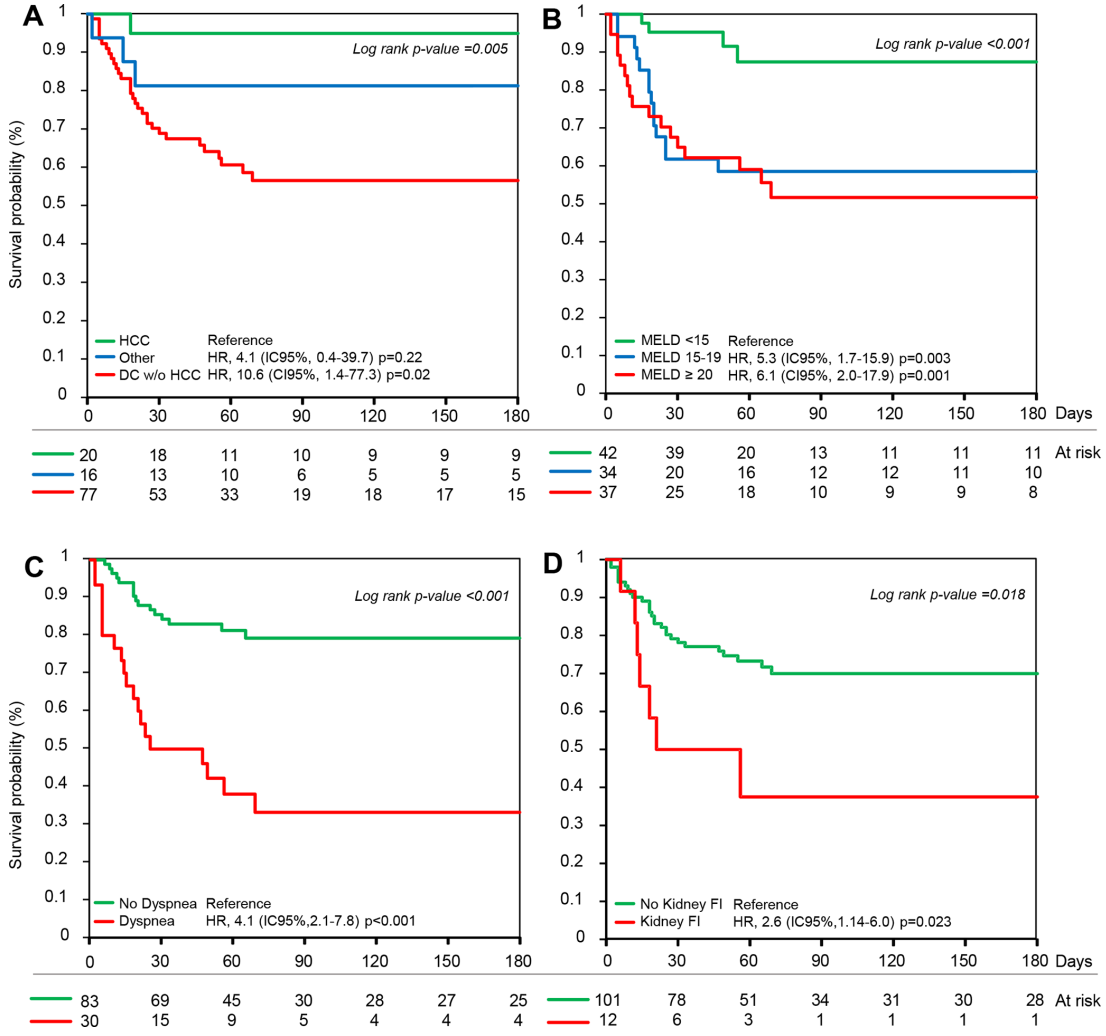


**Figure 2** Kaplan-Meier survival from the date of COVID-19 symptoms stratified by (A) indication for liver transplantation (DC without HCC, HCC, others); (B) MELD score categories; (C) dyspnoea on presentation; and (D) kidney function impairment. DC, decompensated cirrhosis; FI, function impairment; HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease.

and 2 cyclosporine), with mycophenolate–mofetil being used in 21 cases. Survival rate was 96% at a median follow-up of 118 days (IQR 31–170), with a single patient dying from posterior reversible encephalopathy syndrome 82 days after LT.

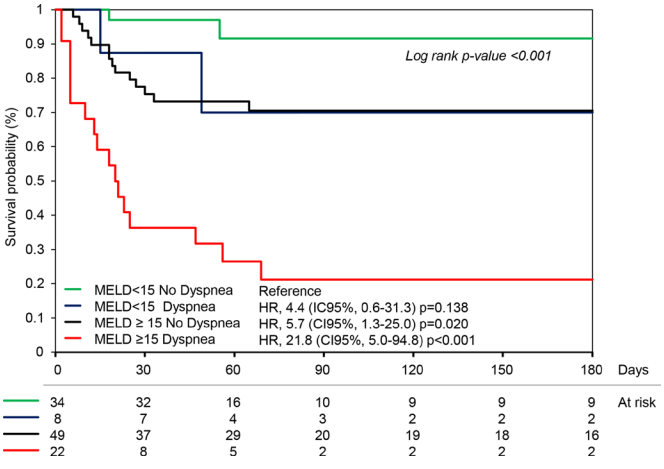


**Figure 3** Kaplan-Meier survival from the date of COVID-19 symptoms stratified by MELD score and dyspnoea on presentation. MELD, Model for End-stage Liver Disease.

## DISCUSSION

This study reports on the first large cohort of patients who developed COVID-19 while listed for LT, and several novel findings regarding pretransplant and post-transplant outcomes were obtained, which are summarised as follows: LT candidates with symptomatic SARS-CoV-2 infection were at high risk of early death, particularly those with DC and Lab-MELD score of ≥15. The mortality risk was dramatically increased in patients with a Lab-MELD score of ≥15 and with dyspnoea on presentation. COVID-19 was confirmed to be a potential trigger of AD and ACLF. Respiratory failure frequently resulted in candidates being ineligible for LT and was the most frequent cause of death. During the two waves of the pandemic, clinical presentation, course and mortality risk from COVID-19 did not significantly change. Finally, short-term survival after LT was 96%, and no cases of SARS-CoV-2 reinfection were observed to date.

In our analysis, liver transplant candidates with COVID-19 showed a 30-day mortality probability which was similar to that observed in a control group of cirrhotic patients hospitalised for AD due to bacterial infection. The overall mortality rate was 32.7% (37/113) and reached 49.2% (31/63) in patients with DC and a Lab-MELD score of >15, which is triple the mortality risk observed in listed patients with comparable Lab-MELD scores without COVID-19.[10] This indicates that liver

**Table 4** Comparison between first and second SARS-CoV-2 waves

| | First wave (February–June 2020) | Second wave (July–November 2020) | |
|---|---|---|---|
| | n=51 | n=62 | P value |
| Age at symptoms (years) | 59 (53–63) | 57 (52–64) | 0.58 |
| Site of highest intensity of care, n (%) | | | |
| Outpatient | 10 (19.6) | 23 (37.1) | 0.093 |
| Ward | 25 (49.0) | 27 (43.6) | |
| ICU | 16 (31.4) | 12 (19.4) | |
| MELD | 17 (14–22) | 15.5 (11–20) | 0.30 |
| Number of comorbidities | 1 (0–2) | 1 (1–2) | 0.23 |
| Symptoms, n (%) | | | |
| Fever>37.2°C | 32 (62.7) | 42 (67.7) | 0.58 |
| Cough | 25 (49) | 39 (62.9) | 0.14 |
| Dyspnoea | 16 (31.4) | 14 (22.6) | 0.30 |
| Fatigue | 5 (9.8) | 14 (22.6) | 0.071 |
| Confusion | 6 (11.8) | 8 (12.9) | 0.86 |
| Diarrhoea | 7 (13.7) | 6 (9.7) | 0.50 |
| Ground-glass opacities, n (%) | 34 (66.7) | 27 (44.3) | 0.018 |
| Respiratory support | 29 (56.9) | 27 (43.6) | 0.16 |
| Acute decompensations, n (%) | | | |
| No | 33 (64.7) | 42 (67.7) | 0.56 |
| Yes | 15 (29.4) | 19 (30.7) | |
| Yes, unrelated to COVID-19 | 3 (5.9) | 1 (1.6) | |
| ACLF, n (%) | | | |
| No | 40 (78.4) | 53 (85.5) | 0.57 |
| Yes | 9 (17.7) | 8 (12.9) | |
| Yes, unrelated to COVID-19 | 2 (3.9) | 1 (1.6) | |
| COVID-19 therapy, n (%) | | | |
| High-dose steroid | 2 (3.9) | 5 (8.1) | 0.45 |
| Low-molecular weight heparin | 8 (15.7) | 21 (33.9) | 0.028 |
| 60-day mortality probability, % (95% CI): overall | 35.3 (23.9 to 50.0) | 25.9 (16.2 to 39.9) | 0.23 |
| 60-day mortality probability, % (95% CI): in hospitalised patients | 43.9 (30.0 to 60.3) | 41.2 (26.5 to 61.0) | 0.72 |
| Cause of death, (%) | | | |
| Respiratory failure | 8 (36.4) | 2 (13.3) | 0.31 |
| Liver failure+respiratory failure | 10 (45.5) | 10 (66.7) | |
| Liver failure without respiratory failure | 3 (13.6) | 1 (6.7) | |
| Other causes+respiratory failure | 1 (4.6) | 2 (13.3) | |

ACLF, acute-on-chronic liver failure; MELD, Model for End-stage Liver Disease.

transplant candidates with DC should rigorously adopt all the usual measures to prevent SARS-CoV-2 infection and evidences the need for rapid implementation of reinforced vaccination programmes since the efficacy of standard vaccines will be likely lower than that reported in the registration studies. This is particularly relevant since the prevalence of COVID-19 in LT candidates was 6.05%, which is double that observed in the general population of similar age,[11] possibly due to higher susceptibility to SARS-CoV-2.

Despite the baseline Lab-MELD score being strongly associated with mortality, COVID-19-related respiratory failure remained the predominant cause of death at 89.2% (33/37), remaining at 10.2% (4/37) due to liver-related complications, these results concurring with previous studies from Europe and the USA.[12–17]

Following multivariable analysis, two factors, namely, dyspnoea on presentation and baseline Lab-MELD score emerged as independent predictors of mortality. Interestingly, patients listed for HCC had a much better outcome than those with DC, most likely because of associated lower Lab-MELD score at listing. The combination of Lab-MELD score of ≥15 and dyspnoea was associated with a negative prognosis, 60-day mortality risk of 68.8% (50.1–85.2), while any other possible combination of these two simple baseline factors allowed an early stratification of the mortality risk, and this may help clinicians in their decision-making. Despite what was observed in other patient cohorts, neither age nor comorbidities influenced the mortality risk, probably due to advanced age and increased comorbidities being exclusion criteria for WL.

COVID-19 led to a marked deterioration in liver function with high rates of AD (33.6%) and ACLF (17.6%) being observed. The occurrence of AD and ACLF in patients with COVID-19 was associated with a mortality risk of 59% and 90%, respectively, which compares unfavourably with the 44% and 65% observed by Marjot *et al*.[16] This finding is probably due to the different prevalence of patients with advanced liver impairment between the two cohorts (Child-Pugh B/C 76% vs 48%). We also compared our cases of ACLF occurring after COVID-19 with those observed in an appropriately balanced cohort of 91 cirrhotic patients who were admitted for AD triggered by bacterial infections. Notably, the mortality after developing ACLF was significantly higher for patients having ACLF triggered by COVID-19 (85% vs 53%), which is explained by the frequent occurrence of refractory respiratory failure in patients with COVID-19 and ACLF (18/20 vs 0/28).

A preliminary comparison between the two waves of the pandemic was possible. The 60-day mortality risk was 35.3% (95% CI 23.9% to 50.0%) during the first wave and did not significantly decline during the second wave (26%, 95% CI 16.2% to 40.2%), with respiratory failure remaining the major cause of death. This suggests that the impact of newly established therapies to control COVID-19[18 19] is limited in patients with advanced liver disease. Patients with prior COVID-19 had favourable outcomes, with early survival of 96% (25/26) after receiving a liver transplant. Median ICU and total hospital stay were 3 (IQR 3–6) and 11 (IQR 8–19) days, which concur with what is observed in more recent series.[20] To date, zero case of SARS-CoV-2 recurrence was observed after LT.

Mortality in the great majority of patients in this cohort was due to respiratory failure (33/37, 89.2%), with respiratory failure being a clear contraindication for proceeding with an LT. Thus, apprehension related to wait-listed patients not receiving a graft for organ unavailability due to a decline in organ donation, and competition for ICU beds seems unfounded. Although, it cannot be excluded that a minority of urgent patients, SARS-CoV-2 negative, may have died on the WL due to a decline in organ offers, being indirect victims of the COVID-19 pandemic.

Two main limitations are to be acknowledged for this study. First, focusing on symptomatic cases with confirmed positive SARS-CoV-2 PCR test despite test sensitivity below 80%, we found that some cases may have inadvertently been excluded. Second, the impact of the COVID-19 pandemic on access to LT could not be measured.

In conclusion, liver transplant candidates with a MELD score of >15 and presenting with COVID-19-associated dyspnoea are at high risk of respiratory failure and early death. Once patients

**Uncited Box 1 Centers participating to the ELITA/ELTR Covid-19 project in liver transplantation including all collaborators at each site**

1. Hepatology and Gastroenterology Unit, ASST GOM Niguarda, Milan, Italy: Luca S Belli, Giovanni Perricone, Raffaella Viganò and Chiara Mazzarelli, General Surgery and Abdominal Transplantation Unit, ASST GOM Niguarda, and School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy: Luciano G De Carlis, Andrea Lauterio and Alessandro Giacomoni. Department of Infectious Diseases Unit, ASST GOM Niguarda, Milan, Italy. Marco Merli, Giovanni Travi and Massimo Puoti.

2. Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy: Federica Invernizzi, Francesca Donato nd Pietro Lampertico.

3. Papa Giovanni XXIII Hospital, Bergamo Italy. Department of Gastroenterology, Hepatology and Transplantation: Luisa Pasulo and Stefano Fagiuoli. Department of Surgery: Marco Zambelli, Michela Guizzetti and Michele Colledan.

4. Internal Medicine Unit of Treatment of Severe Organ Failure, IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico di Sant'Orsola. Maria Cristina Morelli and Giovanni Vitale.

5. Gastro-hepatology Unit: Silvia Martini and Antonio Ottobrelli. Liver Transplantation Center: Damiano Patrono and Renato Romagnoli. Azienda Ospedaliera Universitaria, Città della Salute e della Scienza di Torino, University of Torino, Torino, Italy.

6. Department of Surgery, University of Modena E Reggio Emilia, Policlinico Di Modena, Modena, Italy: Fabrizio Di Benedetto.

7. Ospedale Cisanello, UO Trapiantologia Epatica Universitaria Azienda Ospedaliera, Pisa, Italy: Paolo De Simone, Paola Carrai and Petruccelli Stefania.

8. Unit of Internal Medicine and Hepatology, Department of Medicine, University of Padova Paolo Angeli, Salvatore Piano, Simone Incicco and Nicola Zen.

9. Hepato-bilio-pancreatic Surgery and Transplantation Department, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg: Francoise Faitot and Baptiste Michard.

10. Centre Hepato-Biliaire, AP-HP Hôpital Paul Brousse Hospital, Paris-Sud Saclay University, Villejuif, France: Ilias Kounis, Audrey Coilly, Saliba Faouzi, Rene Adam, Vincent Karam and Didier Samuel.

11. Hôpital Henri Mondor, Service d'Hepatologie, Créteil, France: Christophe Duvoux and Norbert Ngongang.

12. Department of Hepatogastroenterology, Hepatology and Liver Transplantation Unit: Sylvie Radenne, Domitille Poinsot and Celine Guichon; Department of Digestive Surgery and Liver Transplantation: Mickael Lesurtel; Croix-Rousse University Hospital, Hospices Civils de Lyon, University of Lyon I, Lyon, France.

13. Hepatogastroenterology Unit, Hôpital Trousseau, CHRU de Tours, Tours, France: Laure Elkrief.

14. Hôpital Du Kremlin Bicêtre, Sce De Chirurgie Pédiatrique, Le Kremlin Bicêtre, France: Emmanuel Gonzales.

15. The Liver Unit, Queen Elizabeth Hospital Birmingham, Birmingham, UK: Darius Mirza, Thamara Perera and Angus Hann.

16. University of Edinburgh Royal Infirmary, Liver Transplantation Unit, Edinburgh, UK. Gabriel Oniscu and Chris Johnston.

17. Department of HPB and Transplant Surgery, Freeman Hospital, Newcastle upon Tyne, Tyne and Wear, UK: Derek Manaz.

18. Hospital Clinic de Barcelona, General and Digestive Surgery Department, IDIBAPS, CIBERehd, Barcelona, Spain: Costantino Fondevila, Jordi Colmeneroas and David Toapanta.

19. Hospital Universitari Vall D'Hebron, Liver Unit and HBP Surgery and Transplants Department, Barcelona, Spain: Lluis Castells and Ernest Hidalgo.

20. Hospital Gregorio Maranon, Liver Transplant Unit, Madrid, Spain: Magdalena Salcedo Plaza and Fernando Diaz-Fontenla.

21. Liver Transplant Unit, Hospital Virgen del Rocio, Seville, Spain: Jose Maria Alamo.

22. Hospital Universitario Virgen De La Nieves, Servicio de Cirurgia General, Granada, Spain. Esther Brea Gomes.

23. Cirurgia HPB y Transplante Hepatico, Hospital Universitario de Badajoz, Spain: Gerardo Blancoa and Alberto Marcacuzco.

24. Hospital General Universitario De Alicante, Unidad Transplantes Hepatico, Alicante, Spain: Gonzalo Rodriguez and Sonia Pascual.

25. Hospital Universitario 12 de Octubre, HBP And Transplant Unit, General Surgery, Madrid, Spain: Carmelo Loinaz.

26. Division of Transplantation, Department of General Surgery, Medical University of Vienna, Austria: Gabriela Berlakovich, Dagmar Kollmann and Georg Györi.

27. Universitaire Ziekenhuizen Leuven, Abdominal Transplant Surgery, Leuven, Belgium: Jacques Pirenne and Natalie Vandende.

28. Hopital Erasme Universite Libre De Bruxelles, Department of Abdominal Surgery, Brussels, Belgium: Valerio Lucidi.

29. Erasmus MC, Transplant Institute, University Medical Center Rotterdam, Department of Surgery, Division of Hepatobiliary Surgery and Liver Transplantation, Rotterdam, The Netherlands. Wojciech G. Polak; Department of Gastroenterology and Hepatology: Caroline den Hoed.

30. Department of Abdominal Surgery and Transplantation, CHU Liege, University of Liege, Belgium: Olivier Detry.

31. Department of Surgery: Christian Toso; Divisions of Transplantation and of Gastroenterology and Hepatology: Giulia Magini and Nicolas Goossens; Geneva University Hospitals, Geneva, Switzerland.

32. Huddinge Hospital, Department of Transplantation Surgery, Huddinge, Sweden: Bo Goran Ericzon and Carl Jorns.

33. Digestive Diseases and Liver Transplantation Center from Fundeni Clinical Institute, Bucharest, Romania: Liana Gheorghe, Speranta Iacob and Irinel Popescu.

34. Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland: Joanna Raszeja-Wyszomirska and Krzysztof Zieniewicz.

recover from COVID-19, LT is a safe option with no evidence of SARS-CoV-2 recurrence.

**Author affiliations**
[1]Hepatology and Gastroenterology, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
[2]Hepatology, Hopital Henri Mondor, Creteil, France
[3]Research Centre on Public Health (CESP), Universita degli Studi di Milano-Bicocca Scuola di Medicina e Chirurgia, Monza, Italy
[4]Digestive Diseases and Liver Transplantation Center, Institutul Clinic Fundeni, Bucharest, Romania
[5]Epatologia e Gastroenterologia, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
[6]Service Hépatologie et Gastro-Entérologie, Hospital Croix-Rousse, Lyon, France
[7]Research Centre on Public Health (CESP), Università degli Studi di Milano-Bicocca, Milano, Italy
[8]Liver Transplantation Unit, Ospedale Molinette, Torino, Italy
[9]Division of Transplantation, Department of General Surgery, Medical University of Vienna, Vienna, Austria
[10]Department of Surgery, Queen Elizabeth Hospital Birmingham, Birmingham, UK
[11]Gastroenterology and Transplant Hepatology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
[12]Liver Transplant Unit, HPB Surgery and Transplants, Hospital Vall d'Hebron, Barcelona, Spain
[13]Service de Chirurgie Hepatobiliare and Transplantation, Hôpital de Hautepierre, Strasbourg, France
[14]Department of Abdominal Surgery and Transplantation, CHU Liege, University of Liege, Liege, Belgium
[15]Division of Gastroenterology and Hepatology, Policlinico di Milano, Milan, Italy
[16]Division of Abdominal Surgery, Department of Surgery, Geneva University Hospitals, Geneve, Switzerland
[17]Trapiantologia Epatica Universitaria, Ospedale Cisanello, Pisa, Italy
[18]Centre Hépatobiliaire, Hospital Paul Brousse, Villejuif, France
[19]Department of Organ Failures and Transplantation, IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[20]Liver Transplantation Unit, Hospital General Universitario Gregorio Maranon, Madrid, Spain
[21]Transplantation Surgery, Karolinska Institute, Stockholm, Sweden
[22]HBP and Transplant Unit, Hospital Universitario 12 de Octubre, Madrid, Spain
[23]Liver Transplantation Unit, Edinburgh Royal Infirmary, Edinburgh, UK
[24]Digestive Diseases and Liver Transplantation Center, Clinical Institute Fundeni, Bucuresti, Romania
[25]Department of Surgery and Transplanattion, Hospital Croix-Rousse, Lyon, Rhône-Alpes, France
[26]Department of Surgery, Queen Elizabeth Hospital, Birmingham, UK
[27]Department of Gastroenterology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Lombardia, Italy
[28]Centre Hépato-Biliaire, Hôpital Paul Brousse, Villejuif, Île-de-France, France
[29]UMR-S1193, INSERM, Villejuif, Île-de-France, France
[30]Department of Surgery, Geneva University Hospitals, Geneve, Switzerland
[31]Department of General, Transplant and Liver Surgery, Faculty of Medicine, Medical University of Warsaw, Warszawa, Poland
[32]Hepatogastroenterology Unit, Hopital Trousseau, Chambray-les-Tours, France
[33]Centre Hépatobiliaire, Hôpital Paul Brousse, Villejuif, France
[34]Gastroenterology and Hepatology, Rotterdam, The Netherlands
[35]Infectious Diseases, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
[36]Chirurgia Generale e dei Trapianti, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy
[37]Department of Medicine, Faculty of Medicine and Surgery, University of Padua, Padova, Italy
[38]General and Digestive Surgery, Hospital Clinic de Barcelona, Barcelona, Spain
[39]Department of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands

**Twitter** Christophe Duvoux @NONE

**Acknowledgements** The authors thank the European Liver and Intestine Association board members: Ulrich Baumann, Giacomo Germani, Silvio Nadalin, Pavel Taimr, Christian Toso and Krzysztof Zieniewicz for supporting and actively promoting the study; Maruska C Nizzi for linguistic support; and all centres participating in the ELITA/ELTR COVID-19 project in liver transplantation, including all collaborators ateach site (box 1).

**Collaborators** Raffaella Viganò, Chiara Mazzarelli, Andrea Lauterio, Alessandro Giacomoni, Giovanna Travi, Massimo Puoti, Francesca Donato, Pietro Lampertico, Michele Colledan, Marco Zambelli, Michela Guizzetti, Giovanni Vitale, Fabrizio Di Benedetto, Paola Carrai, Stefania Petruccelli,Simone Incicco, Nicola Zen, Baptiste Michard, Saliba Faouzi, Didier Samiuel, Norbert Ngongang, Domitille Poinsot, Celine Guichon, Emmanuel Gonzales, Gabriel Oniscu, Derek Manaz, Jordi Colmenero, David Toapanta, Ernest Hidalgo, Jose Maria Alamo,Esther Brea Gomes, Gerardo Blanco, Alberto Marcacuzco, Gonzalo Rodriguez, Sonia Pascual, Georg Györi, JAcques Pirenne, Natalie Vandende, Valerio Lucidi, Giulia Magini, Nicolas Goossens, Carl Jorns, Irinel Popescu and Joanna Raszeja-Wyszomirska.

**Contributors** LSB: conceptualisation, data curation and drafting and critical revision of the manuscript; RF, PAC and SC: formal analysis and critical revision of the manuscript; CF, WGP, CD and GP: conceptualisation, review and editing, and critical revision of the manuscript; SR, DP, GB, AH, LP, LC, FF, OD, FI, GM, PDS, IK, MCM, FDF, B-GE, CL, CJ, LG, ML, RR, DK, MTPRP, SF, DM, AC, CT, KZ, LE, VK, RA, CdH, MM, MP, LDC, SP, GO and PA: data curation and critical revision of the manuscript; SF and LDC: critical revision of the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

**Patient consent for publication** Not required.

**Ethics approval** Ethical approval was given by clinical research ethics committee from Hospital Clinic Barcelona (ID: HCB/2020/0479).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Contacts:Rita Facchetti, Rita.Facchetti@unimib.it; Paolo Cortesi, Paolo.cortesi@unimib.it; IDOTCOVID platform.



**ORCID iDs**
Luca Saverio Belli http://orcid.org/0000-0001-8714-2439
Paolo Angelo Cortesi http://orcid.org/0000-0001-5241-4473
Giovanni Perricone http://orcid.org/0000-0003-3890-5393
Ilias Kounis http://orcid.org/0000-0003-3876-2097
Fernando Díaz Fontenla http://orcid.org/0000-0002-4700-0281
Renato Romagnoli http://orcid.org/0000-0001-8340-8885
Paolo Angeli http://orcid.org/0000-0002-1913-0716

## REFERENCES

1 Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National hospital discharge survey. *Chest* 2003;124:1016–20.
2 Jalan R, Fernandez J, Wiest R, *et al*. Bacterial infections in cirrhosis: a position statement based on the EASL special conference 2013. *J Hepatol* 2014;60:1310–24.
3 Piano S, Singh V, Caraceni P, *et al*. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. *Gastroenterology* 2019;156:e1310:1368–80.
4 Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014;61:1385–96.
5 Moreau R, Jalan R, Gines P, *et al*. Acute-On-Chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–37. 1437 e1421-1429.
6 Fernández J, Acevedo J, Wiest R, *et al*. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. *Gut* 2018;67:1870–80.
7 Premkumar M, Devurgowda D, Dudha S, *et al*. A/H1N1/09 influenza is associated with high mortality in liver cirrhosis. *J Clin Exp Hepatol* 2019;9:162–70.
8 Jalan R, Saliba F, Pavesi M, *et al*. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol* 2014;61:1038–47.
9 Gray RJ. A Class of $K$-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *Ann Stat* 1988;16:1141–54.
10 Freeman RB, Wiesner RH, Roberts JP, *et al*. Improving liver allocation: MELD and PeID. *Am J Transplant* 2004;4 Suppl 9:114–31.
11 WHO. Available: https://covid19.who.int/table ISS Italy - https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_9-dicembre-2020
12 Bajaj JS, Garcia-Tsao G, Biggins SW, *et al*. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. *Gut* 2021;70:531–6.
13 Hashemi N, Viveiros K, Redd WD, *et al*. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: a multicentre United States experience. *Liver Int* 2020;40:2515–21.
14 Singh S, Khan A. Clinical characteristics and outcomes of coronavirus disease 2019 among patients with preexisting liver disease in the United States: a multicenter research network study. *Gastroenterology* 2020;159:768–71.

15 Qi X, Liu Y, Wang J, *et al*. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. *Gut* 2021;70:gutjnl-2020-321666.
16 Marjot T, Moon AM, Cook JA, *et al*. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. *J Hepatol* 2021;74:33667–9.
17 Iavarone M, D'Ambrosio R, Soria A, *et al*. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020;73:1063–71.
18 Horby P, Lim WS, Emberson JR. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *NEJM* 2020.
19 Beigel JH, Tomashek KM, Dodd LE. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *NEJM* 2020 https://doi.org/10.1056/NEJMo a2007 764
20 Rana A, Witte ED, Halazun KJ, *et al*. Liver transplant length of stay (Los) index: a novel predictive score for hospital length of stay following liver transplantation. *Clin Transplant* 2017;31:e13141.