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# The short-term outcomes of patients with chronic liver disease hospitalized with COVID-19

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**ABBREVIATIONS**

| | |
|---|---|
| ARDS | Acute respiratory distress syndrome |
| BMI | Body mass index |
| CLD | Chronic liver disease |
| COVID-19 | Coronavirus disease 2019 |
| ICU | Intensive care unit |
| IQR | Interquartile range |
| LMWH | low molecular weight heparin |
| MEWS | Modified Early Warning Score 3-4 |
| MV | Mechanical ventilation |
| PCR | Polymerase chain reaction |
| SARS-CoV2 | Severe acute respiratory syndrome corona virus 2 |

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**ABSTRACT**

**Background and aims:** Patients with chronic liver disease (CLD) might have aggravated course upon acquisition of coronavirus disease 2019 (COVID-19). We aimed to analyse the outcomes of patients with CLD who were hospitalized due to COVID-19.

**Methods:** Medical records of 4014 patients hospitalized due to COVID-19 in a regional referral hospital over a 12-month period were analysed. Patients with CLD were identified based on discharge diagnoses according to ICD-10 classification. Patients were followed for 30 days from admission, and their outcomes (intensive care unit (ICU) admission, mechanical ventilation (MV) or death) were analysed.

**Results:** Of the 4014 patients, 110 (2.7%) had CLD and 49 (1.2%) had cirrhosis. Median age of CLD patients was 67.5 years, 79 (71.8%) were males, 224 (23.5%) obese, 56 (50.9%) reported alcohol abuse, 24 (21.8%) had non-alcoholic fatty liver disease, 11 (10%) viral hepatitis and 98 (89.1%) had pneumonia. Median length of hospitalization was 12 days, 32 (29.1%) patients required ICU admission and 23 (20.9%) MV, while 43 (39.1%) died. In univariate analysis, patients with cirrhosis (45% vs 73%, HR=2.95; P<0.001), but not those with non-cirrhotic CLD (74% vs 73%, P>0.05), experienced worse 30-days survival when compared to age, sex and COVID-19 duration matched cohorts. In a logistic regression analysis conducted on the overall and matched cohorts, liver cirrhosis, but not CLD, predicted inferior survival independently of age, comorbidities and severity of COVID-19, with a fourfold higher adjusted risk of 30-day mortality.

**Conclusion:** Cirrhosis is independently associated with higher 30-day mortality of hospitalized patients with COVID-19.

## INTRODUCTION

The involvement of the liver with coronavirus disease 2019 (COVID-19) has attracted a great amount of scientific interest, with somewhat conflicting results reported in terms of their pathogenetic interplay and influence on clinical outcomes (1).

Liver transaminases are frequently elevated in patients with COVID-19, but whether they result from a direct cytopathic effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or as a part of the systemic inflammatory response to infection remains a matter of debate (2-5). In a proportion of patients, they might also be elevated as a result of a drug-induced liver injury. However, elevated liver transaminases, especially AST, have been associated with worse clinical outcomes, including the need for intensive care unit (ICU) admission, mechanical ventilation (MV) and death (2-4). The clinical behaviour and outcomes of patients with existing chronic liver disease (CLD) when they acquire COVID-19 are a completely different issue. Several studies observed a worse outcome in patients with CLD including cirrhosis, whereas others more specifically noted worse outcomes only among patients with decompensated cirrhosis (6-9). On the other hand, those with compensated cirrhosis who acquire COVID-19 have a high chance of experiencing decompensation, leading to a worse overall survival rate (9). Although multicentric, these investigations are not without limitations, as they were heterogenous in terms of the aetiology of CLD and the prevalence of cirrhosis (especially decompensated), and they have not included many racial/ethnic groups. Therefore, the conclusions provided from these reports might not be generalizable to all ethnic groups and geographical regions without additional research.

In the present study we aimed to analyse the clinical outcomes of a cohort of patients with CLD who were hospitalized due to COVID-19 in University hospital Dubrava, Zagreb, the largest regional referral centre in Croatia, representing a Caucasian population of Central-Eastern European ancestry with a prevailing alcoholic aetiology of liver disease.

## PATIENTS AND METHODS

### Patients

We retrospectively analysed data from a large single-institution registry of hospitalized COVID-19 patients. The study included 4.014 patients who were hospitalized during the period March 2020 to March 2021 in the regional referral hospital University Hospital Dubrava Zagreb, which was completely repurposed for the treatment of COVID-19 patients. All patients had a positive polymerase chain reaction (PCR) or antigen COVID-19 test prior to hospital admission. The patients were treated according to the contemporary guidelines, with varying exposure to low molecular weight heparin (LMWH), corticosteroids and remdesivir. The data on the clinical characteristics, laboratory parameters on admission and clinical outcomes during hospitalization were taken from the hospital registry.

### Methods

Patients with chronic liver disease (CLD) were identified based on the International Classification of Diseases-10 (ICD-10) codes of the discharge diagnoses. Data on the aetiology and stage of CLD were retrieved from the medical records of these patients. The presence of decompensated cirrhosis was defined by any of the following signs: ascites, bleeding from gastroesophageal varices, portal encephalopathy and/or icterus (serum bilirubin≥50 umol/L). Patients with transplanted livers were included in the general analyses due to documented pre-COVID-19 clinical and laboratory signs of liver disease. The severity of COVID-19 at admission was classified according to the World Health Organization (WHO) clinical management guidance adopted by the national guidelines for the treatment of COVID-19, version 2, issued on 19 November 2020 by the Ministry of Health (10,11). Patients presenting with severe pneumonia that required oxygen supplementation or a modified early warning score (MEWS) 3-4 (12) were deemed to have severe COVID-19. Those with acute respiratory distress syndrome (ARDS) or MEWS≥5, or the need for ICU treatment or MV were considered to have a critical level of illness. Obesity was defined as a body mass index (BMI) above 30 kg/m$^2$. Comorbidities were evaluated as individual entities and were summarized using the Charlson comorbidity index (13). COVID-19 is associated with an increased incidence of thromboembolic events. As the presence of cirrhosis is also considered a prothrombotic condition, but at the same time is accompanied by higher bleeding risks due to portal hypertension and thrombocytopenia, thrombotic events and major bleeding episodes were

analysed as well (14-16). Venous and arterial thrombotic events were considered if documented by objective imaging or laboratory methods. CT angiography or a colour Doppler ultrasound of deep veins in the lower extremity were used to assess venous thromboembolic events. Both these methods in addition to laboratory derangements compatible with clinical presentation were employed to examine arterial thrombotic events. More detailed information on thrombotic events from our database has been published previously (17). Bacterial sepsis was determined if positive blood cultures were noted. Clinically relevant bleeding was recognized if documented in medical records. The outcomes analysed included 30-day mortality assessed from the date of admission to hospital, as well as a need for ICU treatment and/or MV.

**Statistical methods**

Patients with and without chronic liver disease were compared in overall as well as cohorts matched according to age, sex and day of disease at presentation. Matching was performed using the automated procedure provided by the MedCalc statistical program, controlling for sex and allowing for a difference of two years in age and one day in the day of disease on admission. The two obtained groups were well balanced regarding specific comorbidities and matched parameters, as shown later in the paper. The normality of the distribution was tested using the Shapiro-Wilks test. The numerical variables were non-normally distributed and were presented as the median and interquartile range (IQR). They were compared between groups using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and were compared between groups using the $X^2$ test. Survival analyses were based on the Kaplan-Meier method. Survival curves were univariately compared using the Cox-Mantel version of the log-rank test. Initial data screening was performed using a custom-made MS Excel workbook (18). Multivariate analyses were performed using a logistic regression. P values $<0.05$ were considered statistically significant. All presented analyses were performed using the MedCalc statistical software version 20 (MedCalc Software Ltd, Ostend, Belgium).

**Ethical issues**

This study was conducted in accordance with the World Medical Association Declaration of Helsinki and the protocol was approved by the Institutional Ethics Committee, No. 2020/1012-10. Due to the retrospective design, the requirement for signed informed consent was waived by the Ethics Committee.

## RESULTS

### Demographic data and clinical characteristics of the patients

There were 110 hospitalized COVID-19 patients with CLD identified, amounting to 110/4014 (2.7%) of the total cohort. The median age of the CLD patients was 67.5 years with an IQR (57.3-75), with 79/110 (71.8%) males, and the median disease duration before hospital admission had a three-day IQR (1-8). The most common aetiologies of liver disease were alcoholic liver disease in 52/110 (47.3%), non-alcoholic fatty liver disease in 24/110 (21.8%), viral hepatitis in 11/110 (10%), autoimmune liver disease in 4/110 (3.6%), toxic liver disease in 3/110 (2.7%) and other aetiologies in 16/110 (14.5%). Four patients had transplanted livers. A total of 49/110 (44.5%) patients presented with liver cirrhosis, among whom 7/49 (14.3%) had a Child-Pugh A score, 23/49 (46.9%) Child-Pugh B and 19/49 (38.8%) Child-Pugh C. Considering the total CLD cohort, 61/110 (55.5%) patients had CLD without cirrhosis, 12/110 (10.9%) had compensated cirrhosis and 37/110 (33.6%) had decompensated liver cirrhosis, with a median MELD score of 7, 9.5 and 20 points, respectively ($P<0.001$).

Since the CLD patients were significantly younger (median 67.5 vs 74 years; $P<0.001$), were more likely to be males (71.8% vs 55.8%; $P<0.001$) and presented earlier in the disease course (median three vs five days; $P<0.001$) in comparison to other hospitalized patients in the overall cohort, a case-control matching procedure based on age, sex and disease duration before admission was performed to account for these differences. A total of 110 CLD patients and 110 matched controls were selected, and their clinical characteristics are presented in Table 1.

In comparison to the matched patients, the CLD patients had pneumonia and a severe form of COVID-19 at admission more often ($P<0.05$ for both analyses), whereas there were no significant differences in these parameters between patients with CLD without cirrhosis and those with compensated and decompensated liver cirrhosis ($P>0.05$ for both analyses). Patients with CLD also more frequently reported drinking alcohol, had a higher Charlson comorbidity index, a lower haemoglobin level, lower platelets, higher D-dimers, higher AST, higher GGT, higher ALP, higher total bilirubin, lower albumin and lower Prothrombin time ($P<0.05$ for all analyses). There were no significant differences in the other analysed parameters. The length of hospitalization and a profile of the specific therapies (use of LMWH, corticosteroids and remdesivir) did not significantly differ between patients with and without CLD ($P>0.05$ for all analyses).

**Outcomes**

Rates of ICU admission, need for high flow oxygen therapy and MV, arterial and venous thromboses, bleeding, major bleeding and bacterial sepsis rates did not significantly differ between patients with and without CLD either overall, or in the matched cohorts of patients. The same was observed when mutually comparing patients with CLD without cirrhosis and those with compensated and decompensated liver cirrhosis (P>0.05 for all comparisons).

In terms of 30-day mortality, 43 (39.1%) patients with CLD died. Among the CLD patients without cirrhosis, 15 died from respiratory complications related to COVID-19, one from end-stage gastric cancer and one from massive cerebrovascular insult. Among the patients with compensated cirrhosis, 10 died from respiratory complications related to COVID-19, and one who had severe pneumonia developed liver decompensation and died. Of those who presented with decompensated cirrhosis at admission, 10 died from liver failure, and five from respiratory complications.

Univariate analysis demonstrated the worse survival of CLD patients with cirrhosis in comparison to both non-cirrhotic CLD (survival rates 45% vs 74%; HR=2.46; P=0.004) and control patients (survival rates 45% vs 66%; HR=2.04; P=0.005 compared to overall, and survival rates 45% vs 73%; HR=2.95; P<0.001 compared to matched controls). However, there were no significant differences in the survival of non-cirrhotic CLD patients in comparison to the overall and matched controls (survival rates 74% vs 66% vs 73%, respectively; P>0.05 for both analyses) (Figure 1). Among the patients with liver cirrhosis, there were no significant differences in the 30-day survival rate between those with compensated (N=12) and decompensated (N=37) liver disease (P=0.627), nor regarding the Child-Pugh grade (0.773). CLD patients with a MELD score >7 experienced significantly shorter 30-day survival rates (HR=2.49; P=0.005). No significant difference in 30-day survival was observed among the patients with different aetiologies of CLD (P=0.372), although those with an alcohol-related aetiology of liver disease had a tendency towards worse survival rates (Figure 2). Among the four patients with transplanted livers, two died. Of the four, one had decompensated cirrhosis due to chronic hepatitis B and C coinfection, and was receiving entecavir at the time of admission (died); one had decompensated cirrhosis due to obstruction at biliary anastomosis and was successfully treated by endoscopic dilatation (survived); one had non-alcoholic fatty liver disease of the graft (survived), and one patient acquired COVID-19 in the early post-

transplant period (at day 11), developed left liver lobe necrosis due to arterial thrombosis, as well as gastric perforation, and finally died 39 days after liver transplantation.

We further analysed the associations between CLD and liver cirrhosis with 30-day mortality in a series of logistic regression models adjusted for age, sex, MEWS score and particular comorbidities in both the overall and matched cohorts. The models are shown in Table 2. In both the overall and matched cohorts of patients, liver cirrhosis, but not CLD per se, predicted inferior survival rates independently of age, particular comorbidities and severity of COVID-19 clinical presentation with an approximately fourfold higher-adjusted risk of 30-day mortality.

## DISCUSSION

In this cohort of patients with CLD mostly of an alcoholic aetiology, who were hospitalized due to COVID-19, the presence of liver cirrhosis was associated with the fourfold higher risk of 30-day mortality when compared to the cohort without CLD matched according to age, sex and COVID-19 duration. This association was independent of the age, sex, comorbidity burden and severity of COVID-19 at initial presentation and could not be observed across all stages of CLD, except for cirrhosis.

Whereas elevated liver blood tests (LBT) are frequently observed in those with COVID-19, these patients very rarely develop significant liver injury, including liver failure (1-4). Acute liver failure in this setting usually develops as a part of severe sepsis, septic shock and/or multiorgan failure. Nevertheless, elevated LBT, especially AST, have been associated with worse clinical outcomes of COVID-19, probably reflecting the higher degree of systemic inflammatory response to SARS-CoV2 infection (2). The precise mechanisms of liver affection by COVID-19 are still a matter of debate. Both hepatocytes and cholangiocytes were shown to allow for viral entry into the cells through ACE2 receptors, and for complete viral replication in vitro (19). Yet, reliable evidence of such replication and cellular injury in vivo is lacking. In situ hybridization demonstrated the presence of SARS-CoV2 in 68% of samples in microthrombi and sinusoidal endothelial cells, but another study using deep proteomics failed to establish reliable evidence for viral replication within the liver (20,21). Additionally, an investigation that compared the clinical features of patients suffering from COVID-19 and seasonal influenza found no significant differences in terms of deranged liver biochemistry (22). Therefore, it seems that liver injury results from the immune-mediated generalized response to SARS-CoV2 infection, rather than being a direct cytopathic effect of the virus itself. Liver histopathology might provide better insights, but comprehensive histopathological data are lacking. The largest examination, comprising 48 wedged liver biopsy samples obtained during post-mortem autopsies from patients who died from a severe respiratory form of COVID-19, revealed lesions including microthrombi within the small portal branches, endothelial lesions, fatty transformed hepatocytes (probably at least in part due to pre-existing non-alcoholic fatty liver disease, the derangement of mitochondrial function, mild inflammatory infiltrate and fibrosis in portal tracts, and no biliary injury (20). Based on these

data, and considering the impaired respiratory function and procoagulant features of COVID-19, it seems that the derangement of hepatic blood flow, mitochondrial injury and systemic hypoxia represent a background for liver injury in typical cases of COVID-19. In patients without pre-existing CLD, this kind of liver injury is obviously not sufficient to result in a severe liver impairment that dominates the clinical presentation.

However, a different development could be expected among those with pre-existing CLD, especially in the advanced stages. Patients with CLD have an increased expression of ACE2 receptors, and thus might be more susceptible to SARS-CoV2 infection, but this was not observed in the large populational studies (23). In fact, those with CLD are underrepresented among COVID-19 patients (24,25). It might be assumed that patients with CLD are better aware of the risks of acquiring infection, and therefore avoid social contact, rather than being somehow protected by the presence of liver disease. In any case, upon the acquisition of COVID-19, an incremental decline in the 30-day survival rates of patients with a worsening clinical stage of cirrhosis was reported in previous research (6-8). Patients with cirrhosis, especially of an alcoholic aetiology, have elevated serum levels of inflammatory cytokines, due to increased gut permeability and a higher influx of bacterial endotoxins into the liver via the portal circulation, which in turn activate the immunological compartment residing in the liver. In these circumstances, an additional microbial stimulus, such as infection by SARS-CoV2, causes an excessive overall immune response that may result in a cytokine storm, which, together with the histological changes as described above, predispose cirrhotic patients to adverse clinical outcomes. This observation is supported by our data as well, demonstrating diminished 30-day survival rates in patients with cirrhosis, irrespective of age, sex, comorbidity burden and severity of COVID-19 at the initial presentation. As opposed to this, the risk of dying from COVID-19 was similar among patients with non-cirrhotic CLD and those without CLD, as shown by our results and some other investigations (6-8).

Further dissection of the cirrhotic population led some authors to conclude that mortality is only increased in decompensated patients. In a multinational investigation (covering 29 countries and five continents) which included 745 CLD patients (386 cirrhosis), the overall mortality was 20% in the total CLD cohort, 8% in patients without and 32% in those with cirrhosis (19%, 35% and 51% with Child-Pugh A, B and C respectively) (8). This was also confirmed in a multicentric study from the United States (N=867 patients with CLD, of whom 134 had compensated and 93 decompensated cirrhosis) that found a 2.9 times higher risk of death in decompensated patients as compared to those with compensated cirrhosis and non-cirrhotic

CLD (6). Interestingly, the observed mortality from COVID-19 is similar to that from bacterial infections as previously recorded in cirrhosis, and they likely share similar pathways in causing liver damage (26,27). Hence, after contracting COVID-19 cirrhotic patients are at risk of becoming decompensated, with a high mortality as noted. According to a report from Asia, around 20% of patients with cirrhosis develop decompensation upon the contraction of COVID-19, with a higher mortality among patients with a baseline Child-Turcotte-Pugh score>8 (9). Therefore, patients with compensated cirrhosis and a worse functional stage of liver disease should be closely followed for the signs of decompensation and treated accordingly.

In our cohort we could not find a difference in survival between compensated and decompensated patients, but this was probably the result of the very small group (N=12) of those with compensated cirrhosis, which was insufficient to reach statistical power. In fact, the poor 30-day survival rate observed in the overall cohort of patients with cirrhosis must have been substantially influenced by its unbalanced structure, as decompensation was present in 75% of the analysed patients. Therefore, our data are important as they specifically reflect the biological behaviour of advanced cirrhosis in Caucasian patients of Central-Eastern European ancestry infected by COVID-19, with a prevailing alcoholic aetiology (in 47% of patients) of CLD. Both an alcoholic aetiology and the presence of decompensated cirrhosis were previously reported as being associated with a higher risk of mortality (8). Hence, it was not surprising to observe a high overall mortality of 39% among patients with CLD in general, and 55% among a subset of CLD patients with liver cirrhosis in our cohort. These figures are comparable to the risk of dying from other common insults (with bacterial infections and alcoholic hepatitis in first place) occurring in patients with liver cirrhosis that cause acute liver decompensation (28). Thus, greater efforts should be made to improve prevention (e.g., vaccination and hygiene), in order to significantly reduce the incidence of COVID-19 infection and, subsequently, hospital admissions. This might subsequently warrant better access to healthcare for patients with non-COVID-19 CLD (as for patients with other significant non-COVID-10 diseases, such as cancer), as their increased mortality has also been noted during the COVID-19 pandemic (29,30).

We have not observed an increased risk of thrombotic incidents nor major bleeding among patients with CLD in comparison to the overall cohort and matched controls, although this observation might be biased by the retrospective nature of this investigation, as imaging studies for thromboembolic complications were not part of the regular protocol in patients without the

clinical suspicion of a thrombotic event. However, prophylaxis with LMWH was almost universal and our data confirm its safety even in patients with decompensated cirrhosis.

Interestingly, the only difference in terms of comorbidities between CLD and the matched cohort of patients was a higher prevalence of gastroesophageal reflux disease (GERD)/peptic ulcer disease (PUD) among the patients with CLD, which is in keeping with previous observations of a higher incidence and prevalence of PUD among patients with liver cirrhosis, probably due to the impaired gastric mucosal defence mechanisms (31).

This study has limitations, such as in being retrospective, and including only a limited number of patients with CLD, who were all hospitalized in the tertiary referral centre, thus not covering the entire spectrum of patients with liver disease and varying severity of COVID-19. The proportion of vaccinated patients was very low (25 out of 4014 in the whole dataset, with no vaccinated patients in the CLD subgroup) due to the fact that vaccination had only just started in our country at the time of inquiry. Hence, no meaningful analyses considering vaccination status could be performed. In addition, the number of patients with bacterial sepsis might have been underestimated, as it was defined by the positive blood culture for the purpose of this investigation. Nevertheless, the research included consecutive patients who tested positive for COVID-19 whose medical condition demanded hospital admission, all of whom underwent standardized diagnostic and therapeutic protocols and were followed for the defined period of 30 days from hospital admission. Moreover, the control population was a huge cohort of over 4.000 patients hospitalized in the same hospital due to COVID-19, representative of the Caucasian population of Central-Eastern European ancestry, providing the robust background data. More specifically, our data provide good insight into the course of patients with decompensated cirrhosis and COVID-19, most of whom had an alcoholic aetiology of liver disease.

**In conclusion**, we have demonstrated the diminished survival of cirrhotic patients with COVID-19 in a cohort of Caucasian patients with Central-Eastern European ancestry with a prevailing alcoholic aetiology and decompensated stage of cirrhosis. Patients with non-cirrhotic CLD share the same prospects as other patients suffering COVID-19 but without CLD.

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**Table 1:** Patients' characteristics stratified according to the chronic liver disease status.

| | **Chronic liver disease** | **Controls** | **P value** |
|---|---|---|---|
| Number of patients | 110 | 110 | - |
| Age (years) | 67.5 (57.25 - 75) | 67 (58 - 74) | 0.991 |
| Male sex | 79/110 (71.8%) | 79/110 (71.8%) | 1.000 |
| Body mass index (kg/m$^2$) | 26.1 (24.4 - 30) | 27.7 (25.3 - 32) | 0.166 |
| Arterial hypertension | 67/110 (60.9%) | 72/110 (65.5%) | 0.485 |
| Diabetes mellitus | 32/110 (29.1%) | 27/110 (24.5%) | 0.447 |
| Hyperlipoproteinemia | 20/110 (18.2%) | 27/110 (24.5%) | 0.250 |
| Obesity | 24/102 (23.5%) | 25/104 (24%) | 0.932 |
| Cong. heart failure | 16/110 (14.5%) | 11/110 (10%) | 0.304 |
| Coronary artery disease | 12/110 (10.9%) | 15/110 (13.6%) | 0.538 |
| Previous CVI | 8/110 (7.3%) | 12/110 (10.9%) | 0.348 |
| Previous myocardial infarction | 4/110 (3.6%) | 12/110 (10.9%) | 0.038 |
| Chr. kidney disease | 18/110 (16.4%) | 13/110 (11.8%) | 0.333 |
| **GERD/Peptic ulcer disease** | 36/110 (32.7%) | 19/110 (17.3%) | 0.008 * |
| COPD | 11/110 (10%) | 4/110 (3.6%) | 0.061 |
| Active malignancy | 13/110 (11.8%) | 19/110 (17.3%) | 0.251 |
| History of malignancy | 20/110 (18.2%) | 31/110 (28.2%) | 0.079 |
| **Charlson comorbidity index** | 5 (4 - 7) | 4 (2 - 6) | <0.001 * |
| **Alcohol use** | 56/110 (50.9%) | 6/110 (5.5%) | <0.001 * |
| Smoking | 15/110 (13.6%) | 9/110 (8.2%) | 0.194 |
| Number of drugs in chronic therapy | 6 (3 - 8) | 5 (2 - 7) | 0.066 |
| WBC (x10$^9$/L) | 7.2 (4.7 - 10.1) | 8 (5.68 - 11) | 0.193 |
| **Hemoglobin** (g/L) | 119 (101.25 - 136) | 130.5 (107.75 - 144) | 0.012 * |
| **Platelets** (x10$^9$/L) | 176 (111.25 - 296.25) | 218 (180.25 - 307.75) | <0.001 * |
| CRP (mg/L) | 56.1 (29.83 - 110.8) | 71.7 (27.3 - 137.2) | 0.392 |
| Ferritin (µg/L) | 704.5 (422.25 - 1440.5) | 614 (344 - 1138) | 0.203 |

| | Chronic liver disease | Controls | P value |
|---|---|---|---|
| **D-dimers** (mg/L FEU) | 2 (1.17 - 4.24) | 1.6 (0.74 - 3.7) | 0.049 * |
| Creatinine (mmol/L) | 75.5 (61.25 - 109.5) | 80 (66 - 111) | 0.225 |
| LDH (U/L) | 276 (214.25 - 400) | 299.5 (230.75 - 434.75) | 0.348 |
| **AST (U/L)** | 57 (29 - 106) | 37 (27.25 - 58) | <0.001 * |
| ALT (U/L) | 34 (19 - 58) | 32 (18 - 48) | 0.538 |
| **GGT (U/L)** | 67 (36 - 166) | 43 (27 - 77) | <0.001 * |
| **ALP (U/L)** | 91.5 (63.5 - 151.25) | 74 (57 - 94) | 0.003 * |
| **Total bilirubin (µmol/L)** | 19.1 (12 - 44.13) | 11 (7.6 - 15.95) | <0.001 * |
| Total proteins (g/L) | 61 (56 - 66) | 62 (56 - 65.25) | 0.849 |
| **Albumin** (g/L) | 28 (25 - 32) | 31 (28 - 35) | 0.003 * |
| PT (%) | 94 (83.75 - 102.25) | 101 (94 - 112) | <0.001 * |
| Other infection on admission | 20/110 (18.2%) | 11/110 (10%) | 0.081 |
| Day of disease on admission | 2.5 (1 - 7) | 2 (0 - 7) | 0.939 |
| ECOG status | 3 (1.25 - 4) | 2 (1 - 3) | 0.092 |
| **Pneumonia** | 98/110 (89.1%) | 84/110 (76.4%) | 0.013 * |
| Oxygen therapy | 89/110 (80.9%) | 77/110 (70%) | 0.060 |
| **MEWS severity** | | | Overall P=0.008 * |
| **Mild** | 10/110 (9.1%) | 26/110 (23.6%) | 0.004 * |
| Moderate | 8/110 (7.3%) | 5/110 (4.5%) | 0.391 |
| **Severe** | 84/110 (76.4%) | 65/110 (59.1%) | 0.006 * |
| Critical | 8/110 (7.3%) | 14/110 (12.7%) | 0.178 |
| LMWH thromboprophylaxis | 93/110 (84.5%) | 94/110 (85.5%) | 0.850 |
| Steroid therapy | 76/110 (69.1%) | 79/110 (71.8%) | 0.658 |
| Remdesivir | 6/110 (5.5%) | 13/110 (11.8%) | 0.093 |
| Length of hospitalization | 12 (7 - 21) | 10 (7 - 16) | 0.136 |
| Intensive care unit | 32/110 (29.1%) | 25/110 (22.7%) | 0.281 |
| High-flow oxygen th. | 17/110 (15.5%) | 19/110 (17.3%) | 0.715 |
| Mechanical ventilation | 23/110 (20.9%) | 20/110 (18.2%) | 0.610 |
| Venous thrombosis | 6/110 (5.5%) | 4/110 (3.6%) | 0.748 |
| Arterial thrombosis | 5/110 (4.5%) | 8/110 (7.3%) | 0.391 |
| Bleeding | 10/110 (9.1%) | 11/110 (10%) | 0.819 |
| Major bleeding | 4/110 (3.6%) | 2/110 (1.8%) | 0.409 |
| Bacterial sepsis | 17/110 (15.5%) | 10/110 (9.1%) | 0.153 |
| 30-days mortality | 43/110 (39.1%) | 30/110 (27.3%) | 0.063 |

*Statistically significant at level P<0.05. Numerical variables are presented as median and interquartile range (IQR).

**Table legend.** COPD-Chronic obstructive pulmonary disease; CVI-cerebrovascular insult; ECOG-Eastern Cooperative Oncology Group; GERD-Gastroesophageal reflux disease; LMWH-Light molecular weight heparin; MEWS- Modified Early Warning Score; PT-Prothrombin time (Quick,%); WBC-White blood cell count.

**Table 2:** Logistic regression models for overall and matched patient cohorts for 30-days mortality prediction.

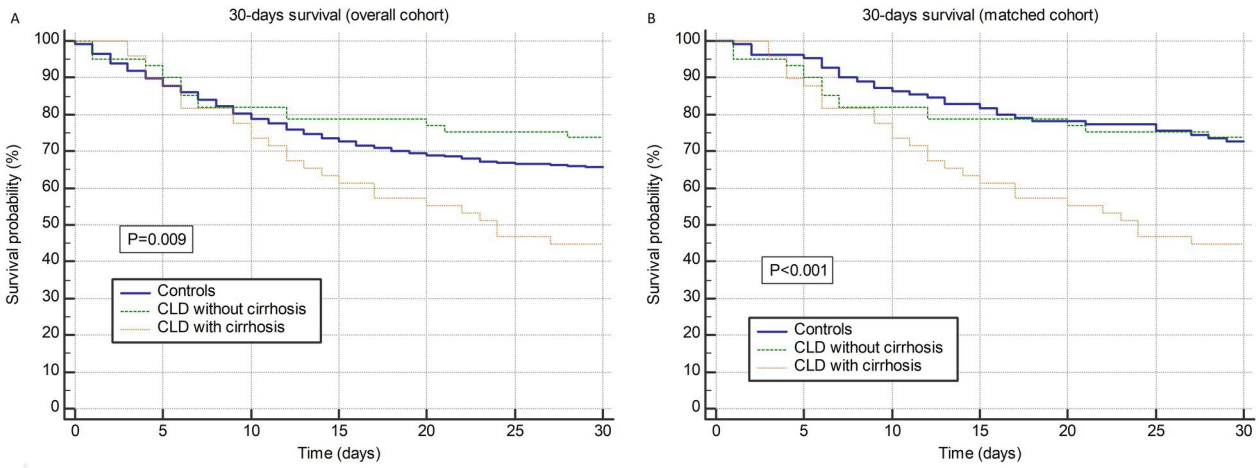
| | **Overall cohort** | | | **Matched cohort** | | |
|---|---|---|---|---|---|---|
| **Covariate** | **P value** | **OR** | **95% CI for OR** | **P value** | **OR** | **95% CI for OR** |
| Age | <0.001 * | 1.075 | 1.066 – 1.084 | 0.001 * | 1.064 | 1.025 – 1.105 |
| **Sex** | 0.001 * | 1.308 | 1.112 – 1.539 | 0.529 | 0.776 | 0.351 – 1.712 |
| **MEWS score** | <0.001 * | 1.614 | 1.540 – 1.691 | <0.001 * | 1.641 | 1.307 – 2.059 |
| Chronic liver disease | 0.383 | 1.335 | 0.697 – 2.558 | 0.996 | 1.002 | 0.423 – 2.369 |
| **Liver cirrhosis** | 0.006 * | 3.712 | 1.447 – 9.525 | 0.003 * | 4.660 | 1.671 – 12.993 |
| Arterial hypertension | 0.563 | 0.944 | 0.777 – 1.147 | 0.547 | 1.309 | 0.544 – 3.151 |
| Diabetes mellitus | 0.065 | 1.179 | 0.989 – 1.406 | 0.765 | 1.142 | 0.475 – 2.746 |
| Hyperlipoproteinemia | 0.937 | 0.992 | 0.819 – 1.202 | 0.762 | 1.155 | 0.452 – 2.945 |
| Obesity | 0.478 | 1.067 | 0.891 – 1.278 | 0.752 | 1.151 | 0.481 – 2.756 |
| Chronic obstructive pulmonary disease | 0.379 | 0.8777 | 0.656 – 1.173 | 0.701 | 0.764 | 0.195 – 2.999 |
| **Chronic kidney disease** | <0.001 * | 1.618 | 1.282 – 2.043 | 0.781 | 1.173 | 0.378 – 3.637 |
| **Chronic heart failure** | <0.001 * | 1.688 | 1.366 – 2.086 | 0.015 * | 4.154 | 1.317 – 13.097 |
| **Active malignancy** | <0.001 * | 2.311 | 1.800 – 2.966 | 0.639 | 1.271 | 0.466 – 3.461 |

*statistically significant at level P<0.05

Table legend. MEWS- Modified Early Warning Score

**Figure 1:** 30-days survival of COVID-19 patients according to the presence of chronic liver disease (CLD) and liver cirrhosis in **A)** an overall cohort and **B)** age-, sex- and duration of the disease at admission- matched cohort.

**Figure 2:** 30-days survival of COVID-19 patients with **A)** liver cirrhosis stratified according to the Child-Pugh grade and **B)** chronic liver disease stratified according to the aetiology.

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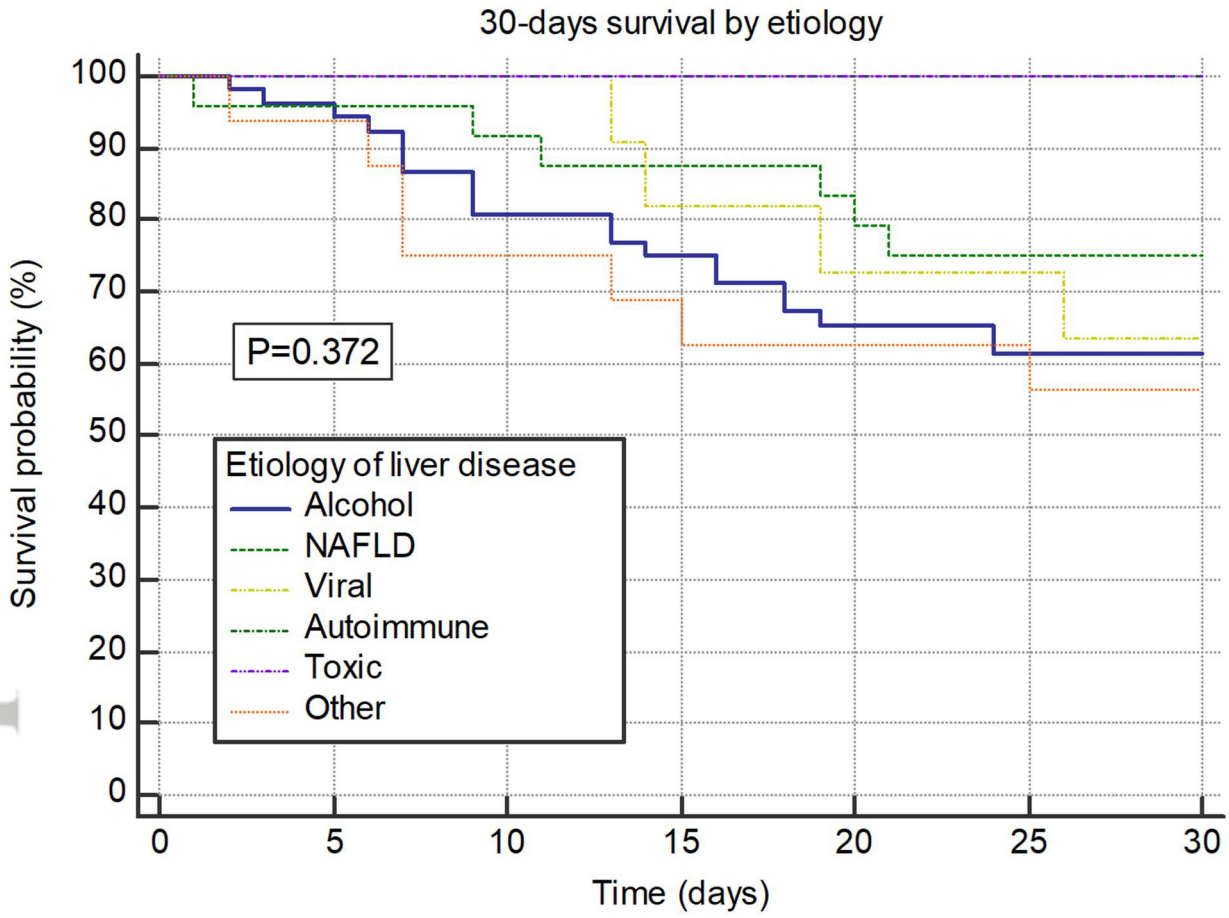


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