



Predictors of clinical outcomes of hospitalized patients with Covid-19: focusing on pre-existing liver disease

Ana Isabel Ferreira¹ · Maria Helena Sarmiento² · Jorge Cotter²

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Abstract

Chronic liver disease is associated with immune system dysfunction, which can lead to a greater risk of infections. Our goal was to assess the impact of chronic liver disease in Covid-19 outcome in hospitalized patients and to identify predictors of the infection's severity. A retrospective case–control study of adult patients hospitalized in Hospital da Senhora da Oliveira–Guimarães, between March 15th 2020 and March 15th 2021, was performed. Demographic factors, clinical and biochemical data were analyzed, as well as the need for oxygen therapy, non-invasive or mechanical ventilation, admission in the intensive care unit and mortality. A total of 336 patients were included, 168 with and 168 without chronic liver disease, with similar comorbidities and pulmonary involvement. Patients with chronic liver disease had a lower percentage of need for oxygen therapy. Regardless of the presence of chronic liver disease, older age, a previously diagnosed pulmonary disease or cardiac condition and more than 25% pulmonary involvement were associated with increased mortality. The need for non-invasive ventilation was higher if the patient was obese, had a previously diagnosed pulmonary disease or had a higher percentage of lung parenchyma involvement. The need for admission in the intensive care unit was associated with obesity and a greater than 25% pulmonary involvement. Chronic liver disease had no impact on Covid-19 severity. Regardless of the presence of chronic liver disease, obesity had an important role in all outcomes except mortality. A higher percentage of lung parenchyma involvement was associated with worst outcomes.

Keywords Chronic liver disease · SARS-CoV-2 infection · Covid-19 · Liver

Introduction

Chronic liver disease (CLD) is associated with immune system dysfunction, which can lead to a greater risk of infections and complications associated to infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the coronavirus disease 2019 (Covid-19) [1]. In addition, patients with hepatic cirrhosis who develop acute respiratory distress syndrome (ARDS), regardless of the cause, have worst prognosis comparing with patients without CLD [2]. However, conflicting data exist concerning the

possibility of CLD being a risk factor for Covid-19 greater severity [3].

Several studies have been performed since the Covid-19 was declared a pandemic by the World Health Organization in March 12, 2020. It has been demonstrated that, in general population, the SARS-CoV-2 infection is associated with liver test abnormalities [4, 5], such as elevations of aspartate-transaminase (AST) and alanine-transaminase (ALT), total bilirubin and prothrombin time (PT) [6–11].

Advanced age, lymphopenia, leukocytosis and elevations of ALT, lactate dehydrogenase (LDH), ferritin, PT and creatinine have been associated with greater mortality [6], as well as decreased levels of platelets and albumin [3–7].

Studies are still scarce, but there are some data indicating that patients with CLD, especially cirrhosis, are more susceptible to worse clinical outcomes, namely Covid-19 with greater severity and greater mortality risk [4, 5, 12].

In an international study including 745 patients, it was demonstrated that a higher CLD stage evaluated by the Child–Turcotte–Pugh score and the alcoholic etiology of the

✉ Ana Isabel Ferreira
ai.voferreira@gmail.com

¹ Department of Gastroenterology, Hospital Senhora da Oliveira–Guimarães, Rua dos Cutileiros 114, Creixomil, 4835-044 Guimarães, Portugal

² Department of Internal Medicine, Hospital Senhora da Oliveira–Guimarães, Rua dos Cutileiros 114, Creixomil, 4835-044 Guimarães, Portugal

CLD were independent risk factors for Covid-19 mortality [13]. On the other hand, chronic hepatitis B virus (HBV) infection does not appear to be associated with increased risk of severe SARS-CoV-2 infection [8]. Patients with non-alcoholic fatty liver disease (NAFLD) or steatohepatitis (NASH) may suffer from metabolic comorbidities such as obesity, hypertension and diabetes mellitus, which are risk factors for a severe course of Covid-19 [6].

The present study aimed to evaluate the impact of CLD in the severity of SARS-CoV-2 infection in hospitalized patients, comparing with a control group with similar comorbidities except the presence of CLD. In addition, we aimed to identify clinical and biochemical parameters that influence the severity of SARS-CoV-2 infection.

Methods

Study design and population

The present single-centered, retrospective case–control study was conducted in Hospital da Senhora da Oliveira–Guimarães, including patients hospitalized for SARS-CoV-2 infection between March 15th 2020 and March 15th 2021. Inclusion criteria were being an adult and having diagnosis of SARS-CoV-2 infection done by a positive result of reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab specimens. Patients with nosocomial SARS-CoV-2 infection were also included. All patients included were not vaccinated for Covid-19. Exclusion criteria included having less than 18 years of age and having been submitted to liver transplant. The hospitalization criteria were those defined by the Directorate-General for Health in Portugal, at the time of hospitalization. The medications used to treat Covid-19 in hospitalized patients were Remdesivir (initial administration of 200 mg in the first day, followed by 4 days of 100 mg per day) and Dexamethasone (6 mg per day during 10 days). This therapeutic was implemented for all hospitalized patients during the analyzed period, according to guidance of the Directorate-General for Health in Portugal. In patients with clinical suspicion of concomitant bacterial infection, it was added antibiotic therapy.

Data collection and outcome measures

Clinical, laboratory and imaging data were collected from electronic medical records, as well as relevant hospitalization outcomes. Clinical data included patient's demographics (age and sex), presence of CLD and comorbid conditions, namely hypertension, diabetes mellitus, hyperlipidemia, obesity, the presence of pulmonary disease, cardiac conditions, renal insufficiency, connective tissue disease and solid

tumors. The percentage of pulmonary involvement described on chest computed tomography (CT) was also described. Laboratory data performed at the time of admission were reported, including white-cell count, neutrophil count, lymphocyte count, platelet count, creatinine, sodium, AST, ALT, total bilirubin, LDH, albumin, ferritin, PT, international normalized ratio (INR) and activated partial thromboplastin time (aPTT). The Charlson Comorbidity Index (CCI), which predicts 10-year survival in patients with multiple comorbidities, was calculated for each patient. Studied outcomes were measurements of disease severity among hospitalized Covid-19 patients with and without CLD, including the need for oxygen therapy, non-invasive ventilation or mechanical ventilation, admission in the intensive care unit (ICU) and all-cause in-hospital mortality.

Study definitions

CLD without cirrhosis was defined as patients with chronic hepatitis B or C, NAFLD, alcoholic liver disease (ALD), hemochromatosis, alpha-1 antitrypsin deficiency, primary biliary cholangitis or primary sclerosing cholangitis, diagnosed previously or during current admission through manual review of laboratory, imaging and/or histopathological data, if present, within last 6 months. Cirrhosis was defined as patients with clinical features and imaging/endoscopy suggestive of chronic liver disease and portal hypertension.

Lung involvement extension in chest CT was defined as mild (less than 25%) or moderate to severe (more than 25%). Covid-19 severity was divided into 4 categories. The first one involved patients that needed hospitalization and/or oxygen therapy and survived, without the need for non-invasive or mechanic ventilation and without being admitted to the ICU. The second category included patients that needed non-invasive ventilation and survived without ICU admission. The third one involved patients that were admitted to the ICU and survived, regardless of the ventilation needs. Finally, the fourth category included patients who died.

Statistical analysis

Categorical variables were described as frequencies and percentages, and continuous variables as mean and standard deviation (SD), since data were normally distributed. Means of continuous variables were compared using independent group *t* tests. Comparison of categorical variables was done using the chi-squared test. A ROC curve was obtained to illustrate the diagnostic ability of continuous variables to predict the all-cause in-hospital mortality. A *p* value < 0.05 was regarded as statistically significant, except for the logistic regressions where a *p* value < 0.1 was considered statistically significant. Statistical analysis software IBM SPSS

version 27.0 (IBM Corp., Armonk, NY, USA) was used for all tests performed.

Results

Study population

From March 15th 2020 and March 15th 2021, 1634 patients with SARS-CoV-2 infection were hospitalized in Hospital da Senhora da Oliveira—Guimarães. From those, 169 with CLD previously diagnosed and an age equal or superior to 18 years were selected, with 1 patient being excluded for being submitted to liver transplant. Therefore, 168 adult patients with CLD and confirmed SARS-CoV-2 infection were enrolled. Posteriorly, from the other group of patients, without CLD previously diagnosed, 168 adult patients were selected, taking into account that they were admitted to the hospital in the same week and had similar comorbidities and similar percentage of pulmonary involvement described on chest CT, as patients with CLD.

A total of 336 patients were enrolled, 168 with and 168 without CLD. Between the groups with and without CLD, no significant differences were identified with regard to sex and the presence of comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, obesity and the presence of pulmonary disease, cardiac conditions, renal insufficiency, connective tissue disease and solid tumors. In addition, there were no significant differences regarding the percentage of pulmonary involvement between the two groups (Table 1).

The main causes of CLD of the patients enrolled in the study were NAFLD in 127 patients (75.6%) and ALD in 31 patients (18.5%). Other minor causes of CLD included were 5 patients with viral hepatitis (3.0%), 2 with hereditary namely hemochromatosis and alpha-1 antitrypsin deficiency (1.2%) and 3 with biliary causes, specifically primary biliary cholangitis and primary sclerosing cholangitis (1.8%). In the CLD population, 24 (14.3%) had cirrhosis.

Impact of CLD in SARS-CoV-2 infection's severity

The CLD group had a lower mean age compared to the group without CLD (65.54 years vs 69.21 years, $p=0.016$). Regarding laboratory analyses performed at the time of admission, the group of patients with CLD had lower mean values for neutrophil count (5 114 vs 6 054, $p=0.015$) and platelets count (195 589 vs 219 636, $p=0.022$). In addition, AST values (69.18 vs 56.80, $p=0.042$), total bilirubin (0.8299 vs 0.4858, $p=0.002$), PT (15.192 vs 13.823, $p=0.031$) and INR (1.340 vs 1.213, $p=0.034$) were significantly higher in the CLD patient group. No significant differences were identified in the mean of the leukocytes

Table 1 Clinical characteristics of patients with Covid-19, with or without CLD

Variable	Total	Without CLD	With CLD	Pearson chi-squared test <i>p</i> value
Sex, <i>n</i> (%)				0.072
Male	208 (61.9)	96 (57.1)	112 (66.7)	
Female	128 (38.1)	72 (42.9)	56 (33.3)	
Hypertension, <i>n</i> (%)				0.357
Yes	222 (66.1)	115 (68.5)	107 (63.7)	
No	114 (33.9)	53 (31.5)	61 (36.3)	
Diabetes, <i>n</i> (%)				0.826
Yes	148 (44.0)	73 (43.5)	75 (44.6)	
No	188 (56.0)	95 (56.5)	93 (55.4)	
Hyperlipidemia, <i>n</i> (%)				0.079
Yes	188 (56.0)	102 (60.7)	86 (51.2)	
No	148 (44.0)	66 (39.3)	82 (48.8)	
Obesity, <i>n</i> (%)				0.163
Yes	110 (32.7)	49 (29.2)	61 (36.3)	
No	226 (67.3)	119 (52.7)	107 (63.7)	
Pulmonary disease, <i>n</i> (%)				0.755
Yes	48 (14.3)	23 (13.7)	25 (14.9)	
No	228 (85.7)	145 (86.3)	143 (85.1)	
Cardiac conditions, <i>n</i> (%)				0.786
Yes	68 (20.2)	35 (20.8)	33 (19.6)	
No	268 (79.8)	133 (79.2)	135 (80.4)	
Renal insufficiency, <i>n</i> (%)				0.645
Yes	20 (6.0)	9 (5.4)	11 (6.5)	
No	316 (94.0)	159 (94.6)	157 (93.5)	
Connective tissue disease, <i>n</i> (%)				0.187
Yes	15 (4.5)	10 (6.0)	5 (3.0)	
No	321 (95.5)	158 (94.0)	163 (97.0)	
Solid tumors, <i>n</i> (%)				0.585
Yes	14 (4.2)	6 (3.6)	8 (4.8)	
No	322 (95.8)	162 (96.4)	160 (95.2)	
% of pulmonary involvement, <i>n</i> (%)				0.063
<25	155 (46.1)	69 (41.1)	86 (51.2)	
>25	181 (53.9)	99 (58.9)	82 (48.8)	

CLD chronic liver disease

count, lymphocytes count, creatinine, sodium, ALT, LDH, ferritin, albumin and aPTT in both groups (Table 2).

In the evaluation of clinical outcomes, patients with CLD had a lower percentage of need for oxygen therapy (78.6% vs 86.9%, $p=0.043$) compared to patients without CLD. There were no significant differences in the percentage of patients needing non-invasive or mechanical ventilation, need for ICU admission and mortality between the two groups (Table 3).

Considering only the major causes of CLD, patients with NAFLD had a higher percentage of need for oxygen therapy (84.3% vs 64.5%, $p=0.013$) compared to patients

Table 2 Age and laboratory characteristics of patients with Covid-19, with or without CLD

Variable	Presence of CLD	<i>n</i>	Mean	SD	Mean standard error	<i>t</i> test <i>p</i> value
Age	No	168	69.21	13.523	1.043	0.016
	Yes	168	65.54	14.371	1.109	
Leukocytes count	No	168	7827.38	4042.820	311.910	0.715
	Yes	168	7554.17	8795.786	678.610	
Neutrophil count	No	168	6054.17	3733.420	288.040	0.015
	Yes	168	5114.29	3274.805	252.657	
Lymphocytes count	No	168	1088.10	503.141	38.818	0.117
	Yes	168	1208.93	861.056	66.432	
Platelets count	No	168	219,636.90	98,578.303	7605.481	0.022
	Yes	168	195,589.29	92,763.580	7156.866	
Creatinine	No	168	1.1911	0.72266	0.05575	0.861
	Yes	168	1.1786	0.58675	0.04527	
Sodium	No	168	136.00	4.216	0.325	0.077
	Yes	168	136.86	4.630	0.357	
ALT	No	168	54.24	52.953	4.085	0.201
	Yes	168	62.20	60.675	4.681	
AST	No	168	56.80	40.490	3.124	0.042
	Yes	168	69.18	67.230	5.187	
Total bilirubin	No	166	0.4858	0.24759	0.01922	0.002
	Yes	165	0.8299	1.41176	0.10991	
LDH	No	168	403.93	328.265	25.326	0.355
	Yes	164	377.05	176.706	13.798	
Albumin	No	112	2.771	0.4844	0.0458	0.236
	Yes	117	2.695	0.4904	0.0453	
Ferritin	No	151	1119.046	1029.6065	83.7882	0.181
	Yes	142	1291.279	1167.6990	97.9911	
PT	No	160	13.823	2.2625	0.1789	0.031
	Yes	163	15.192	7.6478	0.5990	
INR	No	165	1.213	0.2062	0.0160	0.034
	Yes	167	1.340	0.7311	0.0566	
aPTT	No	164	28.187	4.4726	0.3492	0.192
	Yes	165	28.894	5.3047	0.4130	

CLD chronic liver disease, SD standard deviation, ALT alanine-transaminase, AST aspartate-transaminase, LDH lactate dehydrogenase, PT prothrombin time, INR international normalized ratio, aPTT activated partial thromboplastin time. Significant *p* values (<0.05) are highlighted in bold

with ALD. No significant differences were found in the percentage of patients needing non-invasive or mechanical ventilation, needing ICU admission and mortality between the two groups.

Considering only patients with CLD, patients with cirrhosis had a significantly lower percentage of need for oxygen therapy (50.0% vs 83.3%, $p < 0.001$) and for non-invasive ventilation (4.2% vs 22.2%, $p = 0.049$). No significant differences were found in the percentage of patients needing mechanical ventilation or ICU admission and mortality between the two groups.

Clinical and biochemical parameters influencing Covid-19 severity

The mean value of CCI was 4.24 ± 2.47 points. A ROC curve was obtained to predict the all-cause in-hospital mortality with an area under the curve (AUC) of 0.759 ($p < 0.001$) with a sensitivity of 0.978 and a specificity of 0.703 for value of CCI equal or higher than 3 points.

Univariate binary logistic regression analysis revealed associations between Covid-19 outcomes and each categorical and numerical variable under study

Table 3 Clinical outcomes of patients with Covid-19, with and without CLD

Variable	Total	Without CLD	With CLD	Pearson chi-squared test <i>p</i> value
Oxygen therapy, <i>n</i> (%)				0.043
Yes	278 (82.7)	146 (86.9)	132 (78.6)	
No	58 (17.3)	22 (13.1)	36 (21.4)	
Non-invasive ventilation, <i>n</i> (%)				0.591
Yes	70 (20.8)	37 (22.0)	33 (19.6)	
No	266 (79.2)	131 (78.0)	135 (80.4)	
Mechanical ventilation, <i>n</i> (%)				0.332
Yes	18 (5.4)	11 (6.5)	7 (4.2)	
No	318 (94.6)	157 (93.5)	161 (95.8)	
ICU admission, <i>n</i> (%)				0.236
Yes	28 (8.3)	17 (10.1)	11 (6.5)	
No	308 (91.7)	151 (89.9)	157 (93.5)	
All-cause in-hospital mortality, <i>n</i> (%)				0.423
Yes	45 (13.4)	20 (11.9)	25 (14.9)	
No	291 (86.6)	148 (88.1)	143 (85.1)	

CLD chronic liver disease, ICU intensive care unit. Significant *p* values (<0.05) are highlighted in bold

(Supplementary Table S1). However, multiple logistic regression provides a more objective approach for identifying predictors of the Covid-19’s severity. Therefore, a multivariate statistical analysis was performed including

patients with and without CLD, using a multinomial logistic regression model between the Covid-19 severity and the categorical and numerical variables under study (Table 4), except for those with collinearity (leukocytes and INR) and those with high number of missing values (ferritin and albumin). High heterogeneity of Covid-19 severity was observed in the studied population: 72% of patients needed hospitalization and/or oxygen therapy and survived, without the need for non-invasive or mechanic ventilation or ICU admission; 11% of patients needed non-invasive ventilation and survived without being admitted to the ICU; 3% of patients were admitted to the ICU and survived, regardless of the ventilation needs; and 14% died.

Factors that significantly predicted whether the patient needed non-invasive ventilation or only needed hospitalization and/or oxygen therapy, and survived without ICU admission were obesity ($b = -1.45$; Wald $X^2 = 10.02$; $p = 0.002$), the presence of a previously diagnosed pulmonary disease ($b = -1.34$; Wald $X^2 = 5.81$; $p = 0.016$) and a moderate to severe pulmonary involvement described on chest CT ($b = -1.20$; Wald $X^2 = 5.69$; $p = 0.017$).

The odd of a patient needing non-invasive ventilation compared to only needing hospitalization and/or oxygen therapy was 4.26 times higher if the patient is obese patient, 3.82 times higher if the patient has a previously diagnosed pulmonary disease, and 3.31 times higher if the patient had moderate to severe pulmonary involvement.

Table 4 Multinomial logistic regression model between the Covid-19 severity and the significant categorical and numerical variables under study, regardless of the presence of chronic liver disease

	<i>b</i>	Wald X^2	<i>p</i>	Odds ratio	90% CI for odds ratio	
					Lower	Upper
Non-invasive ventilation vs Hospitalization/oxygen therapy						
Obesity	- 1.45	10.02	0.002	0.235	0.111	0.499
Pulmonary disease	- 1.34	5.81	0.016	0.262	0.105	0.654
% of pulmonary involvement	- 1.20	5.69	0.017	0.302	0.132	0.689
Admission to the ICU vs hospitalization/oxygen therapy						
Obesity	- 4.80	9.08	0.003	0.008	0.001	0.113
% of pulmonary involvement	- 2.66	3.70	0.055	0.070	0.007	0.682
AST	0.04	3.93	0.047	1.039	1.006	1.072
aPTT	0.30	4.83	0.028	1.350	1.078	1.689
Mortality vs hospitalization/oxygen therapy						
Pulmonary disease	- 0.95	3.35	0.067	0.386	0.164	0.908
Cardiac condition	- 1.27	5.43	0.020	0.281	0.115	0.688
% of pulmonary involvement	- 0.90	3.48	0.062	0.408	0.185	0.899
Age	0.06	7.89	0.005	1.064	1.026	1.103
AST	0.03	9.30	0.002	1.028	1.013	1.044
ALT	- 0.03	7.77	0.005	0.973	0.957	0.989

$R^2 = 0.419$ (Cox–Snell), 0.509 (Nagelkerke). Model $\chi^2(66) = 170.67$, $p < 0.001$

CI confidence interval, ICU intensive care unit, AST aspartate-transaminase, aPTT activated partial thromboplastin time, ALT alanine-transaminase

Factors that significantly predicted whether the patient was admitted to the ICU and survived, regardless of the ventilation needs, or only needed hospitalization and/or oxygen therapy and survived, without the need for non-invasive or mechanic ventilation or ICU admission were obesity ($b = -4.80$; Wald $X^2 = 9.08$; $p = 0.003$), a pulmonary involvement of more than 25% described on chest CT ($b = -2.68$; Wald $X^2 = 3.70$; $p = 0.055$), the value of AST ($b = 0.04$; Wald $X^2 = 3.93$; $p = 0.047$) and the value of aPTT ($b = 0.30$; Wald $X^2 = 4.83$; $p = 0.028$).

The odd of a patient being admitted to the ICU and surviving compared to only needing hospitalization and/or oxygen therapy was 125 times higher if the patient is obese and 14.29 times higher if the patient had more than 25% pulmonary involvement. Regarding laboratory data, as the AST value increased by a unit, the change in the odd of being admitted to the ICU and surviving (rather than only needing hospitalization and/or oxygen therapy) was 1.04; it was more likely for a patient to need ICU admission if the patient had a higher AST value. As the aPTT value increased by a unit, the change in the odd of being admitted to the ICU and surviving (rather than only needing hospitalization and/or oxygen therapy) was 1.35; it was more likely for a patient to need ICU admission if the patient had a higher aPTT value.

Factors that significantly predicted whether the patient died or not were the presence of a previously diagnosed pulmonary disease ($b = -0.95$; Wald $X^2 = 3.35$; $p = 0.067$) and a previously diagnosed cardiac condition ($b = -1.27$; Wald $X^2 = 5.43$; $p = 0.020$), a moderate to severe pulmonary involvement described on chest CT ($b = -0.90$; Wald $X^2 = 3.48$; $p = 0.062$), the age ($b = 0.06$; Wald $X^2 = 7.89$; $p = 0.005$), the value of AST ($b = 0.03$; Wald $X^2 = 9.30$; $p = 0.002$) and the value of ALT ($b = -0.03$; Wald $X^2 = 7.89$; $p = 0.005$).

The odd of a patient dying was 2.59 times higher if the patient had a previously diagnosed pulmonary disease; 3.56 times higher if the patient had a previously diagnosed cardiac condition and 2.45 times higher if the patient had moderate to severe pulmonary involvement. Concerning age, as age increased by one year, the change in the odd of dying was 1.06; it was more likely for a patient to die if the patient was older. Regarding laboratory data, as the AST value increased by a unit, the change in the odd of dying was 1.03; it was more likely for a patient to die if the patient had a higher AST value. As the ALT value increased by a unit, the change in the odd of dying was 0.97; it was more likely for a patient to die if the patient had a lower ALT value.

Discussion

The prevalence of CLD in patients with SARS-CoV-2 infection has been usually described as less than 5% [14–17], but Hashemi et al. has even reported a prevalence as high as

19% [12]. In our case, between March 15th 2020 and March 15th 2021, 1634 patients were admitted to Hospital Senhora da Oliveira—Guimarães with SARS-CoV-2 infection confirmed by a positive result of RT-PCR in nasopharyngeal swab specimens; of these 168 had CLD, which corresponds to a prevalence of CLD of 10.3% in patients hospitalized for SARS-CoV-2 infection. Posteriorly, from the other group, 168 adult patients without CLD were selected, taking into account that they were admitted to the hospital in the same week. There were no significant differences found between the two groups regarding comorbidities and percentage of pulmonary involvement described on chest CT, allowing for the comparison of laboratory data and clinical outcomes between the two groups.

Hyperbilirubinemia and elevated transaminases (AST and/or ALT) indicate direct or indirect liver damage in patients with Covid-19, regardless of the presence of CLD [14]. The mechanism by which SARS-CoV-2 infection leads to liver damage remains unclear. On the one hand, direct cytopathic effect of the virus has been proposed, due to the abundance of angiotensin-converting enzyme 2 receptors, present in liver and bile duct cells which allows its entry [18]. On the other hand, considering the multisystem involvement of Covid-19, liver damage is likely to be multifactorial with the contribution of systemic inflammation and cytokine release, microvascular thrombosis and alterations in the liver-intestinal axis [19–24]. In the present study, the CLD group had lower mean values for neutrophils and platelets and higher mean values of AST, total bilirubin, PT and INR.

SARS-CoV-2 infection in patients with CLD, especially cirrhosis, appears to trigger a rapid deterioration of liver function, with high rates of CLD decompensation, even in the absence of respiratory symptoms [13]. Regarding the studied outcomes, the need for oxygen therapy was significantly lower in the group with CLD, which may suggest that the need for hospitalization of these patients was more likely due to CLD decompensation.

Data associating a higher mortality of COVID-19 with the presence of DHC are still scarce. However, there are studies that demonstrate a greater severity and mortality of COVID-19 in patients with CLD, especially cirrhotic patients [4, 5, 12, 13]. In our study, the presence of CLD was not associated to worsened Covid-19 outcomes, namely the need for non-invasive or mechanical ventilation, ICU admission and all-cause in-hospital mortality.

Regardless of the presence of CLD, several factors have been associated with an increased risk of mortality from Covid-19. Older age and male gender, as well as the presence of comorbidities such as hypertension, diabetes mellitus, obesity, lung and heart disease were associated with higher mortality [5, 6, 25, 26]. In fact, age alone has been associated with decreased immune response and increased

level of chronic inflammation [27]. Lung disease, particularly chronic obstructive pulmonary disease (COPD), is associated with an increased risk of developing severe disease in the event of any respiratory infection, due to the presence of intrinsic structural damage already existing in the alveoli and bronchi [28]. In the present study, older age, the presence of a previously diagnosed pulmonary disease and a previously diagnosed cardiac condition and a higher percentage of lung parenchyma involvement described on chest CT significantly predicted whether the patient died or needed hospitalization and/or oxygen therapy and survived, without the need for non-invasive or mechanic ventilation and without being admitted to the ICU. The effect of a previously diagnosed cardiac condition was more important than a previously diagnosed pulmonary disease or the presence of more than 25% pulmonary involvement described in chest CT.

Considering laboratory data, lymphopenia, leukocytosis and elevation of ALT, AST, LDH, ferritin, PT and creatinine were associated with higher mortality [3, 4, 6, 17, 22, 26, 29, 30], as well as the decrease in platelet and albumin values [3, 7]. The current study demonstrated that the AST and ALT values significantly predicted the patient's mortality, regardless of the presence of CLD. It was more likely for a patient to die if the patient had a higher AST value and a lower ALT value.

Most studies use all-cause in-hospital mortality as the primary outcome, without taking into account other outcomes, such as the need for non-invasive ventilation and admission to the ICU. This study demonstrated that factors such as obesity, the presence of a previously diagnosed pulmonary disease and a pulmonary involvement of more than 25% had a significant influence on the need for non-invasive ventilation. In addition, a statistically significant association was established between ICU admission and the presence of obesity, a moderate to severe pulmonary involvement described on chest CT, the value of AST and the value of aPTT. It is more likely for a patient to need ICU admission if the patient has a higher AST value and aPTT value. Considering these two outcomes, obesity had the most relevant role.

The APCOLIS study [31] concluded that patients with pre-existing CLD who have Covid-19-related liver injury had an increased risk of liver-related complications, including worsening of jaundice, ascites, hepatic encephalopathy, variceal bleed and spontaneous bacterial peritonitis. These complications were especially frequent in those with lower existing hepatic reserve and previous decompensated cirrhosis.

The present study had several strengths. First, this is the study that includes the largest number of patients with CLD, carried out in a hospital in Portugal. Second, many potential predictors of mortality in Covid-19 patients were included, as well as various outcomes.

The current study also had several limitations. First, it is a retrospective study with patients from a single hospital. Second, data collection was carried out using non-standardized data present in the electronic medical file, with the possibility of underestimating the prevalence of this pathology. In addition, information about alcohol consumption and smoking habits were not available. Finally, histological data were not available for identifying those with mild or advanced fibrosis.

Conclusion

The present study, which included a high number of patients with CLD and a control group with a similar dimension, evidenced that CLD had no impact on Covid-19 severity. Regardless of the presence of CLD, several predictors were associated with different outcomes. Covid-19 mortality increased with older age, the presence of a previously diagnosed pulmonary disease, a previously diagnosed cardiac condition and a higher percentage of lung parenchyma involvement described on chest CT, as well as a higher AST value and a lower ALT value. Besides mortality, the prediction of other degrees of Covid-19 severity was assessed. The need for non-invasive ventilation was influenced by obesity, the presence of a previously diagnosed pulmonary disease and a pulmonary involvement of more than 25% described on chest CT. The need for ICU admission was predicted by the presence of obesity, a moderate to severe pulmonary involvement, higher values of AST and aPTT. A pulmonary involvement of more than 25% described on chest CT was associated with all the studied outcomes. Whereas obesity was a predictor of all the outcomes, except mortality. This is the first study that evaluated predictors of different outcomes compared to needing hospitalization and/or oxygen therapy.

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Author contributions All the authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by AIF. The first draft of the manuscript was written by AIF, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare they have no conflicts of interest.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hospital da Senhora da Oliveira—Guimarães (Date: 30–11-2021/No. Ref: 105/2021).

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