ORIGINAL PAPERS

Liver manifestations in COVID-19 and the influence of pre-existing liver disease in the course of the infection

María Fernanda Guerra Veloz[1], Patricia Cordero Ruiz[1], María José Ríos-Villegas[2], Pilar del Pino Bellido[1], José Bravo-Ferrer[2], Rocío Gálvez Cordero[3], María Lorena Cadena Herrera[1], Carmen Vías Parrado[1], Francisco Bellido Muñoz[1], Francisco Vega Rodríguez[1], Ángel Caunedo Álvarez[1], Jesús Rodríguez-Baño and Isabel Carmona Soria[1]

[1]Gastroenterology and Hepatology Clinical Management Unit and [3]Internal Medicine Unit. Hospital Universitario Virgen Macarena. Sevilla, Spain. [2]Infectious Diseases, Microbiology and Preventive Medicine Clinical Unit. Hospital Universitario Virgen Macarena. Department of Medicine. Universidad de Sevilla - Instituto de BioMedicina de Sevilla (IBiS). Sevilla, Spain

Received: 18/11/2020 · **Accepted:** 11/12/2020

Correspondence: María Fernanda Guerra Veloz. Gastroenterology Department. Hospital Universitario Virgen Macarena. C/ Dr. Fedriani, 3. 41007, Sevilla, Spain. **e-mail:** maferguerrita@hotmail.com

ABSTRACT

Introduction: patients with advanced chronic liver disease (CLD) may be at an increased risk of a severe course due to cirrhosis-associated immune dysfunction. The aim of this study was to determine the prevalence of CLD in COVID-19 patients and to analyze the course of the infection, compared with patients with non-liver disease.

Materials and methods: this was a retrospective single center study of all patients with a positive SARS-CoV-2 polymerase chain reaction (PCR) test from March 23rd to April 30th, 2020. Clinical and biochemical data of patients with and without CLD and COVID-19 were collected from the medical records.

Result: four hundred and forty-seven patients with a SARS-CoV-2 positive PCR were included, 6.3 % had CLD; 69.7 % of patients with CLD were male, with a median age of 65.5 years and active alcohol consumption and smoking; 75 % had non-advanced liver fibrosis and most had non-alcoholic fatty liver disease (NAFLD). The hospital admission rate (92.9 % *vs* 47.7 %, p < 0.001), concomitant comorbidities (diabetes 38.5 *vs* 16.5 %, p = 0.011; obesity 30.8 *vs* 8.5 %, p = 0.033; cancer 23.1 *vs* 5 %, p = 0.027; and chronic obstructive pulmonary disease (COPD) 19.2 *vs* 9 %, p = 0.009) and concomitant antibiotics treatment (19.3 *vs* 5 %, p = 0.018) were higher in patients with CLD than in those without CLD. Inpatient hospital mortality rates were similar in both groups (30.8 *vs* 19.6 %, p = 0.289). The presence of CLD was not associated with mortality (OR = 1.06; 95 % CI = 0.35-3.18; p = 0.924). However, patients with CLD and COVID-19 who were male, obese or under concomitant antibiotic treatment had the highest risk of mortality according to the univariate analysis.

Conclusion: patients with CLD had a higher risk of hospital admission, with worse outcomes during the COVID-19 infection associated to other concomitant comorbidities and a suspicion of bacterial co-infection.

Keywords: SARS-CoV-2. Chronic liver disease. Advanced fibrosis. Hospital admission rate. Mortality.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which rapidly spread worldwide (1). Males, older adults and patients with certain comorbidities are at risk of a

Financial support statement: this study was partly supported by Plan Nacional de I+D+i 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Spanish Ministry of Science and Innovation, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0001), co-financed by the European Development Regional Fund "A way to achieve Europe", Operative Program Intelligence Growth 2014-2020.

Author's contributions:
Concept and design: María Fernanda Guerra, Patricia Cordero Ruiz, Isabel Carmona and Jesús Rodríguez-Baño.
Data collection: Pilar del Pino Bellido, María Lorena Cadena, Carmen Vías Parradas, Rocío Galves Cordero, Francisco Muñoz Bellido and Francisco Vega Rodríguez.
Statistical analysis: María Fernanda Guerra.
Writing of the article: María Fernanda Guerra, Patricia Cordero and Isabel Carmona.
Critical revision of the manuscript: Ángel Caunedo, María José Ríos, José Bravo Ferrer and Jesús Rodríguez-Baño.

Guerra Veloz MF, Cordero Ruiz P, Ríos-Villegas MJ, del Pino Bellido P, Bravo-Ferrer J, Gálvez Cordero R, Cadena Herrera ML, Vías Parrado C, Bellido Muñoz F, Vega Rodríguez F, Caunedo Álvarez Á, Rodríguez-Baño J, Carmona Soria I. Liver manifestations in COVID-19 and the influence of pre-existing liver disease in the course of the infection. Rev Esp Enferm Dig 2021;113(2):103-109

DOI: 10.17235/reed.2020.7627/2020

severe disease course (2). Patients with CLD may be at an increased risk of infection and/or severe course, due to the cirrhosis-associated immune dysfunction (3).

Similar to other coronaviruses, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors to enter into alveolar epithelial cells via endocytosis. The ACE2 protein is found at high levels in the colon, biliary system and liver (4). This could justify the direct liver damage caused by active viral replication in hepatic cells. Some studies showed that 14 to 53 % of patients hospitalized with COVID-19 infections had elevated serum liver markers, primarily elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and slightly elevated bilirubin (5-7). However, there are many factors that may influence the alteration of the liver biochemical profile such as a pre-existing undiagnosed liver disease, liver toxicity treatment or severe COVID-19.

The aim of this study was to determine the prevalence of CLD in patients with a positive SARS-CoV-2 polymerase chain reaction (PCR) test in our health area. Furthermore, the course of COVID-19 in admitted patients with CLD *vs* non-liver disease was analyzed. Finally, the alterations in the liver biochemical profile during COVID-19 in patients with CLD was evaluated.

MATERIALS AND METHODS

Study design

A retrospective single center study that included all positive SARS-CoV-2 PCR patients from March 23rd to April 30th, 2020 in the Hospital Universitario Virgen Macarena (Sevilla, Spain) was carried out. The diagnosis and clinical management of patients with COVID-19 were performed in accordance with the practice guidelines issued by the Spanish health system and internal protocol. Antibiotic treatment was only administered in patients with a suspicion of a bacterial co-infection, according to physician and analytical criteria. A confirmed case of SARS-CoV-2 was defined by a positive result of the real-time reverse transcription PCR assay of a specimen collected via a nasopharyngeal swab.

Data collection

Demographic variables, comorbidities and blood test results of patients with a positive SARS-CoV-2 PCR, with or without CLD, were collected using the electronic medical records. COVID-19 treatment, the need for intubation and intensive care admission, death and length of stay were also recorded.

CLD was considered as: chronic hepatitis B or C, alcohol-related liver disease, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis and non-alcoholic fatty liver disease (NAFLD). This was determined by historical medical records, radiology or analytical records within the last 24 months before the COVID-19 infection. Undiagnosed NAFLD was based on clinical records via: a) non-consumption of alcohol; b) ultrasound with hepatic steatosis regardless of grade in the last 12 months; and c) negative hepatitis B, C and HIV tests.

Advanced liver fibrosis/cirrhosis or non-advanced liver fibrosis was evaluated according to international criteria (8). Child-Pugh-Turcotte (CPT) and the Model for End-Stage Liver Disease (MELD) for cirrhotic and non-invasive assessment of liver fibrosis (fibrosis 4 calculator FIB-4) for NAFLD patients were calculated before and within 12 months of the diagnosis of COVID-19.

The evolution of the liver function tests (LFTs) was examined in both groups. Normal LFT values were considered as ALT/ALT level ranges above 40 IU/l for both genders and values over 40 IU/l were considered as abnormal liver function test. The grade of hepatocellular liver injury was defined using the common terminology criteria for adverse events and evaluated on admission or the peak. Grades 0 to 3 were based on multiples of gender-specific upper limits of the normal (ULN) range (grade 1 = ALT or AST 1-3 ULN, grade 2 = 3-5 ULN and grade 3 > 5 ULN).

Ethical approval

This study was approved by the Research Ethics Committee of the Hospital Virgen Macarena and was performed following good clinical practice guidelines. The collected data were handled confidentially using an anonymous database that was only accessed by the researchers involved in the study, in accordance with current Spanish laws.

Statistical analysis

Qualitative variables were reported as percentages and frequencies. Quantitative variables were reported as the mean and standard deviation (SD) in cases of a normal distribution, and the median and interquartile range (IQR) in cases of a skewed distribution. Differences between patients, with or without CLD, were tested for statistical significance using the Chi-squared test and a p-value of 0.05 was used as the statistical significance level. Univariate binary logistic regression was used to determine the association of each independent variable (factors) with mortality. The odds ratio (OR) and 95 % CI were obtained for variables that were statistically significant in the model. An independent variable with a p-value less than 0.10 was included in the multivariate analysis. The analysis was performed using SPSS 25 (IBM Corporation).

RESULTS

Demographic characteristics whole cohort

Four hundred and forty-seven SARS-CoV-2 PCR were included in the study (Fig. 1) and CLD was present in 6.3 % (28) of the cohort. Patients with CLD were more likely to be male (69.7 %), with a median age of 65.5 (58-74) years, with active alcohol consumption (21.4 %) and smokers (14.3 %). Patients with CLD exhibited more hypertension (60.7 % *vs* 30 %, p = 0.001), diabetes (39.3 % *vs* 10 %, p < 0.001), obesity (28.6 % *vs* 10 %, p < 0.001), congestive heart failure (17.9 % *vs* 4.3, p = 0.010) and chronic obstructive pulmonary disease (COPD) (17.9 % *vs* 2.7, p = 0.010) (Table 1).

Among the patients with CLD, 25 % (7) had advanced liver fibrosis and most were compensated cirrhosis (CTP A),

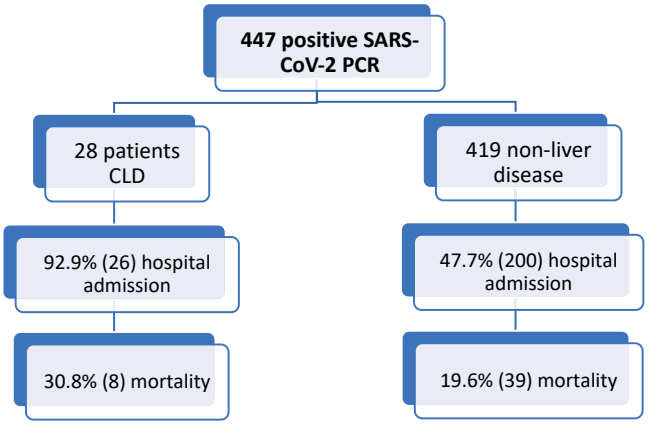

Fig. 1. *Flow chart of patients with a positive SARS-CoV-2 polymerase chain reaction (PCR) with and without CLD and their principal outcome (hospital admission and mortality).*

Table 1. *Demographic characteristic of all patients positive for SARS-CoV-2*

	CLD n = 28 (%)	No-CLD n = 419 (%)	p
Sex, male (%)	19 (67.9)	171 (40.8)	0.005
Age, median (IQR)	65.5 (58.3-73.8)	54 (39-70)	0.002
Active alcohol use (%)	6 (21.4)	6 (1.4)	< 0.001
Smoker (%)	4 (14.3)	12 (2.9)	0.013
Comorbidities n (%)			
Cancer	6 (21.4)	18 (4.3)	0.002
Hypertension	17 (60.7)	126 (30.1)	0.001
Congestive heart failure	5 (17.9)	18 (4.3)	0.010
COPD	5 (17.9)	9 (2.1)	0.001
Diabetes	11 (39.3)	42 (10)	< 0.001
Obesity	8 (28.6)	21 (5)	< 0.001

CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease.

with a MELD score above 15 (Table 2). Four patients had hepatitis C virus (HCV) related cirrhosis; two were HCV-RNA positive without follow-up in our clinic. Two patients had recently been admitted to hospital. One due to variceal bleeding with a *de novo* diagnosis of multicenter hepatocellular carcinoma with portal invasion and the other due to encephalopathy and refractory ascites. Among patients without advanced fibrosis, the principal etiology was NAFLD and 42.9 % (9) of these patients had a regular follow-up in our clinic. Patients with advanced liver fibrosis were younger, with a mean age of 58 (SD 9.69) years and underlying COPD (57.2 %). Meanwhile, patients with CLD without advanced liver fibrosis were older, with a mean age of 68 (SD 12.08) years, and had multiples comorbidities (hypertension 71.4 % and diabetes 47.6 %).

Patients with CLD had increased hospital admissions (92.9 % *vs* 47.7 %, p < 0.001) than those without CLD. The

Table 2. *Demographic and clinical characteristics of patients with SARS-CoV-2 and CLD*

	CLD (28)
Etiology of liver disease	
HCV (SVR)	2 (7.1)
Alcohol-related	2 (7.1)
Alcohol-HCV/active	2 (7.1)
HIV-HCV coinfection	1 (3.6)
Primary biliary cholangitis	1 (3.6)
NAFLD	20 (71.4)
Advanced fibrosis	7 (25)
Non-advanced fibrosis	21 (75)
Basal liver function:	
CPT	
A5- A6	5 (71.4)
B7-B9	2 (28.6)
MELD	
7-9	6 (85.7)
≥ 15	1 (14.3)
Active HCC *(yes)*	2 (28.6)

CLD: chronic liver disease; HIV: human immunodeficiency virus; HCV: hepatitis C virus; NAFLD: non-alcoholic fatty liver disease; CPT: Child-Pugh-Turcotte; MELD: Model for End-Stage Liver Disease.

most common symptoms of COVID-19 in CLD patients were fever (71.4 %), cough (32.1 %) and dyspnea (28.6 %).

Admitted patients' characteristics with and without CLD

There was no difference in age or gender between patients admitted to the hospital with or without CLD. Active alcohol consumption and smoking were more frequent in patients with CLD (Table 3). Some associated comorbidities (diabetes [38.5 *vs* 16.5 %, p = 0.011]; obesity [30.8 *vs* 8.5 %, p = 0.033], cancer [23.1 *vs* 5 %, p = 0.027] and COPD [19.2 *vs* 9 %, p = 0.009]) were more frequent in patients admitted with COVID-19 and CLD. There were no significant differences in respiratory support, the rate of intensive care admission and the median stay length between both groups (Table 3). Intermediate care unit admission was more frequent in patients with CLD. Concomitant antibiotic treatment was more frequent in patients with CLD than in those without (19.3 *vs* 5 %, p = 0.018).

Pattern of LFT over the course of the disease in admitted patients with and without CLD

There were no significant differences in the median levels of D-dimer, ferritin, leucocytes and lymphocytes in patients with or without CLD (Table 3). The median levels of AST and ALT on admission were slightly higher in patients with CLD *vs* those without CLD; 52 (26.7-84) IU/l and 30 (20-51) IU/l *vs* 46 (34-76) IU/l and 26 (16.8-48.5) IU/l, respectively. However, no significant differences were found.

Table 3. *Demographic characteristic of admitted patients with SARS-CoV-2, with or without CLD*

	Chronic liver disease n = 26 (%)	No liver disease n = 200 (%)	p
Sex, male (%)	18 (69.2)	107 (53.5)	0.094
Age, median (IQR)	65.5 (58.5-73.25)	63 (47-73.75)	0.327
Alcohol use (%)	6 (23.1)	4 (2.0)	< 0.001
Smoker (%)	4 (15.4)	3 (1.5)	0.004
Comorbidities n (%)			
Cancer	6 (23.1)	16 (8.0)	0.027
COPD	5 (19.2)	8 (4.0)	0.009
Diabetes	10 (38.5)	33 (16.5)	0.011
Obesity	8 (30.8)	17 (8.5)	0.033
Hospital admission			
Intensive Care Unit	3 (11.5)	28 (14.0)	0.507
Intermediate care unit	5 (19.2)	6 (3.0)	0.004
Respiratory support			
Invasive mechanical ventilation	2 (7.7)	19 (9.5)	0.555
CPAP or non-invasive positive pressure	5 (19.2)	38 (19.0)	0.577
Treatment			
Hydroxychloroquine	22 (84.6)	172 (86)	0.520
Lopinavir/ritonavir	21 (80.8)	164 (82)	0.529
Tocilizumab	2 (7.7)	7 (3.5)	0.277
Corticosteroid	7 (26.9)	49 (24.5)	0.476
Antibiotics	5 (19.3)	10 (5)	0.018
Hospital stay days	8 (5.25-14.75)	7 (5-13)	0.696
Admission median (IQR)			
D-dimer (ug/ml)	1,007 (445-2,347)	764 (458.75-1,486)	0.355
Ferritin (ng/ml)	984.5 (390.43-1,465.75)	757.1 (335.15-1,355)	0.575
Lymphocytes/ul	965 (655-1,247.5)	1,070 (830-1,590)	0.118
AST (U/l)	52 (26.7-84)	46 (34-76)	0.862
ALT (U/l)	30 (20 -51)	26 (16.8- 48.5)	0.349
Liver injures (%)			
ALT > 40	8 (30.8)	58 (29)	0.523
AST > 40	5 (19.2)	54 (27)	0.274
Peak AST median (IQR)	60 (37-91)	83 (50-127)	0.139
AST > 40 (%)	8 (30.8)	78 (39)	0.076
Grade 1	6 (23.1)	55 (27.5)	
Grade 2	1 (3.8)	9 (4.5)	0.928
Grade 3	1 (3.8)	14 (7)	
Peak ALT median (IQR)	61 (45.4-72.5)	76 (37.5-141)	0.461
ALT > 40 (%)	12 (46.2)	82 (41)	0.077
Grade 1	10 (38.5)	44 (22)	
Grade 2	1 (3.8)	19 (9.5)	0.152
Grade 3	1 (3.8)	19 (9.5)	

CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Table 4. *Analysis of comorbidities associated with mortality in patients with COVID-19*

Admitted patients	Univariate		Multivariate	
	OR (95 % CI)	p	OR (95 % CI)	p
Sex (male)	1.56 (0.82-2.98)	0.177	1.53 (0.73-3.19)	0.261
Hypertension	1.28 (0.67-2.43)	0.455	2.20 (0.91-5.33)	0.081
Congestive heart failure	5.79 (2.03-16.51)	0.001	5.66 (1.64-19.54)	0.006
Coronary artery disease	5.03 (1.82-13.89)	0.002	4.95 (1.51-16.27)	0.008
COPD	5.02 (1.60-15.74)	0.006	5.28 (1.48-18.86)	0.010
Cancer	2.05 (0.78-5.41)	0.147	1.99 (0.66-5.93)	0.220
Diabetes	1.89 (0.89-3.99)	0.097	1.71 (0.69-4.22)	0.247
Obesity	1.23 (0.46-3.26)	0.685	1.30 (0.41-4.12)	0.651
CLD	*1.82 (0.74-4.50)*	*0.192*	*1.06 (0.35-3.18)*	*0.924*
Age (median 73 [61-80])	1.030 (1.009-1.051)	0.005	1.018 (0.996-1.040)	0.104

CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease.

The rate of patients who presented abnormal LFTs on hospital admission was similar in patients with and without CLD (ALT = 30.8 % *vs* 29 %, p = 0.523; AST = 19.2 % *vs* 27 %, respectively) (p = 0.274). During the COVID-19 course, patients with CLD had a slightly higher abnormal LFT (ALT >40 46.2 *vs* 41 %) than those without liver disease; most followed the criteria of grade 1 of liver injury (Table 3). On admission, CLD patients with abdominal LFT had a higher median level of D-dimer than those without CLD. However, none were associated with intensive care admission, invasive ventilation or mortality.

Mortality analysis

The mortality rate in admitted patients was similar between both groups, 30.8 % in patients with CLD *vs* 19.6 % in patients without (p = 0.289). The mortality rate was higher in patients with advanced fibrosis *vs* non-advanced fibrosis (50 *vs* 25 %). Three patients with advanced fibrosis died: one due to uncontrolled variceal bleeding, the second had severe pulmonary hypertension caused by severe respiratory failure and the third had COPD, active alcohol consumption and positive RNA-HCV caused by severe respiratory failure. All patients without advanced fibrosis (5) died from severe respiratory failure; four had COPD and two had active pulmonary cancers. Among the CLD patients, the main cause of death was respiratory failure, in 87.5 %.

In the multivariate analysis the presence of CLD was not associated with mortality (OR = 1.06; 95 % CI = 0.35-3.18; p = 0.924) (Table 4). Mortality was analyzed between patients with and without CLD by univariate analysis. Sex (male OR = 11.20; 95 % CI = 1.25-100.31; p = 0.031), the presence of obesity (OR = 7.20; 95 % CI = 1.13-45.96; p = 0.037) and antibiotic concomitant treatment (OR = 12; 95 % CI = 1.95-73.97; p = 0.007) were associated with mortality in patients with CLD and COVID-19 (Table 5).

Table 5. *Analysis of predictors of mortality in patients with CLD and COVID-19*

	Univariate OR (95 % CI)	p
Age	0.989 (0.954-1.026)	0.562
Sex (male)	11.20 (1.25-100.31)	0.031
Smoker	12.67 (0.99-162.26)	0.051
COPD	5.25 (0.90-30.70)	0.066
Cancer	5.25 (0.90-30.70)	0.066
Obesity	7.20 (1.13-45.96)	0.037
Antibiotic treatment	12.00 (1.95-73.97	0.007
Abnormal LFT (admission)	2.03 (0.38-10.69)	0.406
Ferritin	1.000 (0.999-1.000)	0.655

CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease; LFT: liver function tests.

DISCUSSION

The prevalence of CLD in our cohort was 6.8 %, which is consistent with international data (9-11). However, most of our patients followed the NALFD criteria (75 %) and only seven (25 %) patients had cirrhosis. Unlike the Asian cohort etiology (12), there were no cases of chronic hepatitis B in our cohort. This highlights the burden of CLDs in different regions.

Our study showed that patients with CLD and COVID-19 had more associated comorbidities such as cardiovascular diseases, cancer, diabetes, obesity and COPD than those without CLD. Most of these comorbidities were also risk factors associated with poor COVID-19 outcomes in the general population. One of our most important results was that more than 90 % of patients with CLD were admitted to the hospital, which denotes that CLD should be considered as another risk factor for hospital admission.

Our study demonstrated that patients with CLD and COVID-19 had a worse clinical outcome in comparison with patients without liver disease. There was no significant statistical difference in mortality (30.8 *vs* 19.6 %, p = 0.289) in admitted patients with and without CLD; a 30.8 % rate of

mortality is considered as clinically relevant. Patients with cirrhosis are known to have immune function abnormalities and systemic inflammation, which is the pathophysiological hallmark of increased susceptibility to bacterial infection (3). It is also known that patients with cirrhosis have a high risk of contracting a severe course of some virus infection such as influenza, including the development of organ failure, secondary infections and death (13). However, the rate of mortality in the influenza outbreak during the winter of 2017/2018 in the German study in admitted cirrhotic patients was lower than our mortality (18 [13] *vs* 30.8 %).

A recent Italian study compared the mortality rate in admitted cirrhotic patients with COVID-19 *versus* a retrospective cohort of hospitalized cirrhotic patients with bacterial infections. Overall, the Italian mortality was higher in patients admitted with COVID-19. Moreover, they showed that COVID-19 (HR 3.594, 95 % CI 1.465-8.819, p = 0.005) was an independent predictor of mortality (14). However, there was no data on the role of factors (smoker status, active alcohol consumption, comorbidities) that potentially influence the mortality rate when admitted cirrhotic and non-cirrhotic patients with COVID-19 were compared. According to the multivariate analysis in our cohort, the presence of CLD was not associated with mortality such as the presence cardiovascular diseases. However, when mortality between patients with and without CLD was analyzed, gender (male), obesity and antibiotic therapy were risk factors associated with mortality in the subgroup of patients with COVID-19 and CLD.

Another recent international report of 152 patients (103 with cirrhosis) showed that the mortality rate correlated with baseline CTP and the MELD score. Cirrhotic patients with CTP B and C had the highest mortality rate (15). Although this data suggests a strong correlation between decompensated cirrhosis and a high risk of mortality in patients with COVID-19, there are some data that should be highlighted. In this study, the main cause of death in patients with cirrhosis was associated with respiratory failure (78.7 %) and liver-related problems (12.2 %) (15). Given the small number of cirrhotic patients in our cohort, we were not able to find any predictor of mortality in this subgroup. Nevertheless, we showed that patients with advanced liver fibrosis were younger with a higher rate of COPD. Thus, explaining the reason why most of our patients died from severe respiratory injury rather than hepatic decompensation.

Recently, some studies have suggested that NAFLD is an independent risk factor for severe COVID-19 across all ages (16,17). Some studies suggest that hepatic and systemic immune responses caused by NAFLD contribute to the cytokine storm in younger patients with COVID-19. However, in the elderly population, other comorbidities such as coronary heart disease and COPD were more prevalent and any association with NAFLD might be masked by their impact (16). Due to the limited number of patients with CLD included in the study, we were unable to analyze mortality in the subgroup of patients with NAFLD. However, we showed that patients with CLD without advanced liver fibrosis (most were NAFLD) were older with multiple comorbidities. We believe that the high risk of COVID-19 mortality in these patients was associated with age and the concomitant comorbidities such as the presence of obesity and diabetes. In this scenario, the presence of NAFLD could play an important role, adding an already stressed immune system with a baseline liver injury (18). Recently, the criteria for NAFLD have changed and now include the presence of type 2 diabetes mellitus, overweight/obesity and metabolic dysregulation as part of the new diagnosis of metabolic dysfunction-associated fatty liver disease (22). This is in accordance with our results, showing that this type of patients had the highest risk of severe COVID-19.

Regular co-administration of antibiotic treatment was not recommended in the standard management of these patients. In fact, antibiotic treatment was only given when a bacterial co-infection was suspected, according to the medical and analytical criteria of the physicians (less than 10 % of the whole cohort). During hospital admission, patients with CLD and COVID-19 needed four times more antibiotic therapy than those without CLD. Thus, demonstrating that immune dysfunction in cirrhotic patients and some associated comorbidities, including diabetes, can contribute to the risk of bacterial co-infection. Schütte A et al. (13) showed that the risk of developing secondary bacterial infections during an influenza outbreak was higher in admitted patients with liver cirrhosis compared to patients without (82 % *vs* 24 %, p = 0.001).

Abnormal LFTs are common in patients with COVID-19 and it has been reported that 16-53 % of patients have elevated ALT/AST during the course of illness (6,7,19). In our study, over 30 % of patients with CLD and COVID-19 had abnormal LFTs on admission. However, there were no significant differences between those patients without CLD. Although COVID-19 patients with CLD had slightly higher abnormal LFTs, it was not directly associated with a risk of intensive care admission or mortality. An Italian paper analyzed LFTs in patients with COVID-19 admitted in the regular ward, showing that abnormal LFTs on admission strongly predicted worse clinical outcomes (20), with higher intensive care admission and mortality. However, although their patients with abnormal LFTs had a higher rate of comorbidities, they could not find significant differences in the rate of normal *versus* abnormal LTFs in patients with CLD.

Another Asian paper showed that older men with a higher body mass index and underlying liver diseases (21) had a greater rate of abnormal LFTs. Those patients with abnormal LFTs on admission had a higher odds of progressing to severe disease. In our study, admitted COVID-19 patients with CLD and abnormal admission LFTs had higher median levels of D-dimer, which could be associated with major systemic inflammation and a risk of severe disease.

Our study has some limitations, mainly due to the retrospective design, wide inclusion criteria and the different approaches in the first wave, where some symptomatic patients were not tested. This justifies the limited number of patients with CLD included in our study, most with NALFD without regular follow-up. Furthermore, we were unable to perform a multivariate analysis of factors related with mortality in patients with or without CLD, due to the low number of patients included. Furthermore, we were unable to perform subgroup analyses. Most of the data were collected from medical records, which may mean that important data that could be obtained from direct patient interview has been missed. Another weakness is that we only considered the value of the transaminases as abnor-

mal LFTs, due to the lack of other data from liver function tests. Only transaminases were included in the blood test protocol in patients with COVID-19. In conclusion, we provide data showing a higher risk of hospital admission and worse outcome in patients with other concomitant comorbidities and those with a suspicion of bacterial co-infection.

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506. DOI: 10.1016/S0140-6736(20)30183-5
2. Li LQ, Huang T, Wang YQ, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020;92(6):577-83. E-pub Mar 23rd, 2020. PMID: 32162702; PMCID: PMC7228329. DOI: 10.1002/jmv.25757
3. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014;61:1385-96. DOI: 10.1016/j.jhep.2014.08.010
4. Sun J, Aghemo A, Forner A, et al. COVID-19 and liver disease. Liver Int 2020;40(6):1278-81.
5. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol 2020;5(6):529-30. DOI: 10.1016/S2468-1253(20)30084-4
6. Li J, Fan J-G. Characteristics and mechanism of liver injury in 2019 coronavirus disease. J Clin Transl Hepatol 2020;8(1):1-5. DOI: 10.14218/JCTH.2020.00019
7. Wang Y, Liu S, Liu H, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. J Hepatol 2020;73(4):807-16. DOI: 10.1016/j.jhep.2020.05.002
8. Shah AG, Lydecker A, Murray K, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1104-12. DOI: 10.1016/j.cgh.2009.05.033
9. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5(5):428-30. DOI: 10.1016/S2468-1253(20)30057-1
10. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061-9. DOI: 10.1001/jama.2020.1585
11. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323(20):2052-9. DOI: 10.1001/jama.2020.6775
12. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20. DOI: 10.1056/NEJMoa2002032
13. Schütte A, Ciesek S, Wedemeyer H, et al. Influenza virus infection as precipitating event of acute-on-chronic liver failure. J Hepatol 2019;70:797-9. DOI: 10.1016/j.jhep.2018.11.015
14. Lavarone 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(5):1063-71. DOI: 10.1016/j.jhep.2020.06.001
15. Moon AM, Webb GJ, Aloman C, et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: preliminary results from an international registry. J Hepatol 2020;S0168-8278(20)30305-6. DOI: 10.1016/j.jhep.2020.05.013
16. Zhou YJ, Zheng K, Wang XB, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: a multicenter preliminary analysis. J Hepatol 2020;73(3):719-21. DOI: 10.1016/j.jhep.2020.04.027
17. Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. J Hepatol 2020;73(2):451-3. E-pub Apr 8th, 2020. PMID: 32278005; PMCID: PMC7141624. DOI: 10.1016/j.jhep.2020.03.044
18. Chen Y, Varghese Z, Ruan XZ. The molecular pathogenic role of inflammatory stress in dysregulation of lipid homeostasis and hepatic steatosis. Genes Dis 2014;1(1):106-12. DOI: 10.1016/j.gendis.2014.07.007
19. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606. DOI: 10.1136/bmj.m606
20. Piano S, Dalbeni A, Vettore E, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. E-pub Jun 11th, 2020. Liver Int 2020;40(10):2394-406. DOI: 10.1111/liv.14565
21. Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. J Hepatol 2020;73(3):566-74. DOI: 10.1016/j.jhep.2020.04.006
22. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158(7):1999-2014.e1. DOI: 10.1053/j.gastro.2019.11.312