The role of liver steatosis as measured with transient elastography and transaminases on hard clinical outcomes in patients with COVID-19

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***Abstract*:** Liver injury has been widely described in patients with Coronavirus disease 2019 (COVID-19). We aimed to study the effect of liver biochemistry alterations, previous liver disease, and the value of liver elastography on hard clinical outcomes in COVID-19 patients. We conducted a single-center prospective observational study in 370 consecutive patients admitted for polymerase chain reaction (PCR)-confirmed COVID-19 pneumonia. Clinical and laboratory data were collected at baseline and liver parameters and clinical events recorded during follow-up. Transient elastography [with Controlled Attenuation Parameter (CAP) measurements] was performed at admission in 98 patients. All patients were followed up until day 28 or death. The two main outcomes of the study were 28-day mortality and the occurrence of the composite endpoint intensive care unit (ICU) admission and/or death. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were elevated at admission in 130 patients (35%) and 167 (45%) patients, respectively. Overall, 14.6% of patients presented the composite endpoint ICU and/or death. Neither ALT elevations, prior liver disease, liver stiffness nor liver steatosis (assessed with CAP) had any effect on outcomes. However, patients with abnormal baseline AST had a higher occurrence of the composite ICU/death (21% *versus* 9.5%, $p = 0.002$). Patients ⩾65 years and with an AST level > 50 U/ml at admission had a significantly higher risk of ICU and/or death than those with AST ⩽ 50 U/ml (50% *versus* 13.3%, $p < 0.001$). In conclusion, mild liver damage is prevalent in COVID-19 patients, but neither ALT elevation nor liver steatosis influenced hard clinical outcomes. Elevated baseline AST is a strong predictor of hard outcomes, especially in patients ⩾65 years.

Keywords: ALT, AST, controlled attenuation parameter, CAP, liver injury

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Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020; by 13 October 2020, 37,423,660 cases resulting in at least 1,074,817 deaths have been reported to the World Health Organization.[1] The most common symptoms of COVID-19 are fever and cough; some patients can develop pneumonia, with rapid

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acute respiratory failure or acute respiratory distress syndrome.[2–4] Aside from lung damage, there is wide evidence of other organ involvement, including liver disease, with an increased related mortality.[5–11]

Different aspects of liver involvement have been described. Liver injury is present in between 14–76% of affected patients. There may be several different causes and patients with severe COVID-19 seem to have higher levels of aminotransferases.[2–6,12,13] In addition, liver damage has been related to a prolonged hospital stay;[14,15] however, this was not confirmed in another multicenter study.[16]

The effect of previous liver disease has also been evaluated in an American registry study where 250 patients were compared by propensity matching to patients without known liver disease.[7] Patients with previous liver disease (including cirrhotic and non-cirrhotic patients) experienced higher levels of hospitalization and mortality rates compared with patients without previous liver disease.

Other studies have focused on the effect of metabolic associated fatty liver disease (MAFLD) on COVID-19 clinical outcomes in Asian populations.[8–10] Different approaches have been used, combining computed tomography (CT) and consensus diagnostic criteria,[9,10,17] or the clinical index, hepatic steatosis index (HIS) and ultrasound examination.[8] All these studies have shown that patients with MAFLD are at higher risk of severe COVID-19, but that there are key differences between patient subgroups. In the Zhou *et al.*[9] study, the risk was only present in younger patients; while for Zheng *et al.*,[10] in a study evaluating only patients with MAFLD, the risk of severe COVID-19 was greater in obese patients. However, the limited number of patients, the use of different diagnostic criteria, and the selection of the laboratory values to build the diagnostic scores obtained up to one year before the COVID-19 episode make the results difficult to interpret. In that sense, the incorporation of liver elastography to objectively explore liver disease might be a useful tool in the evaluation of liver injury in COVID-19 patients.

The aims of our present study were: (1) to describe the characteristics of liver alterations in COVID-19 patients; (2) to assess the prognostic significance of preexisting liver disease; and (3) to explore the prognostic value of liver elastography, including steatosis measurement, in COVID-19 patients.

Methods

Patient data

After the beginning of the COVID-19 pandemic in Spain on January 31th, the first cases were admitted in our hospital during the first week of March 2020. The Liver Unit of Hospital Universitari Vall d'Hebron started to take care of COVID-19 patients from March 16th in progressively increasing numbers, peaking on March 31st with five hospital wards and around 150 patients. We started a prospective database of all admitted patients from the emergency room on 17 March 2020, with it ending on 17 April 2020. All patients had COVID-19 pneumonia and were confirmed positive by in-house polymerase chain reaction (PCR) tests. No exclusions were determined. At that time, the standard drug therapy for COVID-19 during the whole study period in our hospital was the combination of lopinavir-ritonavir (400 mg bid × 7 days) + hydroxychloroquine (400 mg bid × 5 days) + azithromycin (500 mg qd × 3 days). Other off-label drugs (corticosteroids, cyclosporine, tocilizumab) were administered on an individual basis by patients' physicians in some of the more severe cases; respiratory and circulatory supportive therapy was administered when necessary. All patients were followed-up until day 28 or death.

The database included epidemiological, clinical, laboratory, and outcome parameters that were gathered by all members of the Liver Unit COVID-teams. Collected laboratory parameters at admission included total lymphocyte count, platelet count, ferritin, lactate dehydrogenase (LDH), D-Dimer (DD), interleukin-6 (IL-6), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (AP) and albumin. In addition, follow-up parameters for patients with liver alterations were recorded. The final database was re-checked by each person responsible for entering the data, while a final check was performed by four members of the team.

Given the exceptional circumstances in which the study was conducted, informed consent was

obtained verbally, and incorporated to the electronical medical records for each patient. The study was approved by the ethics committee of our institution (PR(AG)184/2020).

Definitions and outcomes

Prior liver disease was defined by prior clinical history data (before the index admission) indicating a previous diagnosis of a chronic liver disease. Cirrhosis was defined as per usual clinical, histological or elastography criteria.

Liver steatosis was evaluated by the Hepatic Steatosis Index [HSI = 8 × (ALT/AST) + body mass index (BMI) (+2 if type 2 diabetes yes, +2 if female)], using clinical and laboratory data at admission. The usual HSI categories were used to estimate the presence (HSI > 36) or absence (HSI < 30) of steatosis. In patients undergoing transient elastography (TE) (see below), steatosis was defined when the Controlled Attenuation Parameter (CAP) value was above the usual 250 dB/m threshold. In addition, a sensitivity analysis defining steatosis as CAP > 300 dB/m was conducted.

Aminotransferase elevations were defined by AST or ALT values above the upper limit of normality (ULN) (ULN, >50 U/ml for men, >35 U/ml for women). Moderate AST/ALT alteration was categorized in those cases with AST/ALT over 4 times ULN, or acute hepatitis if values of ALT were above 10 times ULN. In patients with at least a moderate increase in transaminase values, a comprehensive work-up was carried out, including viral serologies [hepatitis B surface antigen (HBsAg), anti-hepatitis B core antigen (anti-HBc) immunoglobulin M (IgM), anti-Hepatitis C virus, anti-Hepatitis E virus IgM, anti-cytomegalovirus IgM and anti-Epstein Barr virus IgM), and serum proteinogram, immunoglobulin G levels, and antinuclear autoantibodies for the assessment of autoimmune hepatitis. Concomitant medications were reviewed, and the Roussel Uclaf Causality Assessment Method was used to assess the causal relationship with medications in cases with potential drug-induced liver injury.[18]

The two main outcomes of the study were death at 28 days and composite endpoint intensive care unit (ICU) admission or and/or death at 28 days. ICU admission criteria included the need for ventilator support in the form of high-flow cannulas or intubation (depending on ICU resources, which were constantly adapting) and the absence of any other conditions that might associate a poor short-term prognosis.

Transient elastography

Transient elastography (TE) was used to study the potential role of liver stiffness measurements (LSMs) and liver steatosis on outcomes and their potential value for prediction of the composite endpoint death/ICU. For this specific purpose, LSMs were carried out only in consecutive admitted patients during the first 48 hrs after admission who were in stable condition without oxygen support or with mild-moderate O_2 needs (Sa: $FiO_2 > 300$). The number of LSMs performed was not preplanned and we tried to complete as many as possible. The TE device utilized (Fibroscan 502 Touch) came available with M and XL probes, which were used based on device requirements. The usual quality criteria [at least 10 valid measurements and an interquartile range (IQR)/mean (M) ⩽ 30%] were applied.

Statistics

Differences between categorical variables were assessed by Chi–square test or Fisher's exact test when necessary. Continuous variables were compared using the Student's *t* test or Mann–Whitney test as appropriate. A two-sided *p*-value < 0.05 was considered statistically significant.

In order to adjust the weight of AST by other well-known risk factors on COVID-19 outcomes, two approaches were taken. Firstly, an exploratory adjustment using logistic regression analysis was performed. The selection of variables used to enter the logistic regression models was based on currently available literature, as well as on the results of univariate analyses. For this specific purpose, the composite death and/or ICU was preferred over death. This is due to the larger number of events and because it was regarded as a more realistic and complete representation of the whole effect of COVID-19; both for the individual patient and more globally for healthcare systems. Age and O_2 saturation at admission were maintained as the main covariates for adjustment based on their observed weight on outcomes, as well as on available literature; and, most specially, on their potential utility for rapid and objective triage, even in community settings. In order to

further adjust the weight of AST with other well-documented blood prognostic markers available at admission (lymphocyte count, ferritin, LDH, IL-6, and DD), several combinations of these biomarkers were introduced in blocks of three (while always keeping age and O_2 saturation in the model). Relevant comorbidities with $p < 0.10$ at univariate analyses (hypertension, type-2 diabetes) were also tested (keeping the other main covariates in the model). In order to avoid overfitting and given the total number of events of the composite endpoint, the two most stable variables were used to further adjust odd's ratio (OR) estimates for AST on the composite endpoint.

Secondly, a classification and regression tree (CART) analysis was conducted in order to study and illustrate the interaction between the same variables studied in the logistic regression analyses, as well as to identify the best cut-offs for continuous variables. The method has been previously used by our group and others and has been described extensively elsewhere.[19–21] In brief, the method allows for the construction of inductive decision trees through strictly binary splitting. This method is especially adept at detecting relevant interactions between variables and allows for the identification of subgroups of patients that share a specific combination of clinical characteristics and a similar prognosis. In our study, the number of patients in terminal nodes was set to a minimum of 25 in order to maximize the stability of estimates. Age was forced (as continuous variable) as a first node variable for the reasons mentioned above. Cut-off points for continuous and ordinal variables were generated automatically by the model based on statistical cost assumptions.

Finally, correlation between continuous variables was studied by linear regression, and logarithmic transformations were applied when required by differences in scale of variables in order to allow for a better visual interpretation of results. All analyses were performed using PAWS Statistics (version 19.0; SPSS Inc., Hong Kong) software.

Results

Baseline characteristics and main outcomes

Demographics. During the study period, 370 patients with confirmed COVID-19 were consecutively admitted to the Liver Unit-COVID wards. Table 1 summarizes the baseline characteristics and main outcomes of this cohort. As seen, there was an even distribution between men and women. Their median age was 56 (range 21–88), two-thirds were of white European origin, and most of the remaining patients had Latin-American origin.

Hepatic involvement

Only 33 patients (9%) had previously known liver disease. The etiology of the previous liver disease was MAFLD in 20 (of these four had a mixed etiology with alcohol liver disease), five chronic hepatitis C, five alcohol (four mixed with MAFLD), three chronic hepatitis B, one primary biliary cholangitis (PBC), one biliary tract atresia, one cryptogenic, and one iron deposition disease. Seven of the 33 patients had liver cirrhosis, and only one had decompensated cirrhosis before admission.

TE was performed in 101 patients, from whom three determinations were non-valid. Among the 98 patients with valid TE measurements, the median liver stiffness was 4.7 kPa (range 2.1–22.5) and only two patients had liver stiffness >10 kPa. The median CAP was 252 (range 100–397) and 47 patients (48%) had a CAP value >250 dB/m indicative of steatosis. The HSI was calculated for the whole cohort, and 46% had a value of HSI > 36, suggestive of liver steatosis.

ALT and AST were elevated at admission in 130 patients (35%) and 167 (45%) patients, respectively; while 253 patients (69%) presented with AST greater than ALT. Twenty-five (6.8%) patients presented a moderate ALT elevation during admission: 15 (60%) were male and the median age was 55 years (range 23–73). The peak ALT value of these patients was 268 U/ml (range 160–470). Two (8.3%) patients had a history of underlying liver disease (one MAFLD, one PBC). Seven (28%) presented a moderate increase in ALT at admission to hospital and the rest developed it during hospitalization. In 11 cases (44%), the ALT increase was attributed to COVID-19 infection due to negative findings at the comprehensive work-up of other causes. In the remaining 14 patients, the liver alteration was considered multi-factorial and probably related to different treatments. The most commonly reported medications were parenteral nutrition with three cases and tocilizumab with two. Only two patients met the criteria of acute hepatitis (10 × ULN): in one

Table 1. Main characteristics of the entire cohort.

Variable	*N* = 370
Male	181 (49.0%)
Age (years) (%)	56 (21–88)
Origin	
Europe (%)	252 (68.1%)
South America (%)	102 (27.6%)
Africa (%)	10 (2.7%)
Asia (%)	6 (1.6%)
Diabetes mellitus (%)	58 (15.7%)
Hypertension (%)	121 (33.7%)
Dyslipidemia (%)	89 (24.1%)
BMI (kg/m^2)	28.6 (18.2–42.7)
Days of fever before admission	7 (0–30)
Obese (%)	129 (34.9%)
Previous liver disease (%)	33 (8.9%)
Cirrhosis (%)	7 (1.9%)
Risk alcohol consumption† (%)	16 (4.3%)
AST at admission (U/l)	39 (11–413)
ALT at admission (U/l)	31 (5–420)
AST elevation at admission (%)	167 (45.1%)
ALT elevation at admission (%)	130 (35.1%)
Moderate AST elevation anytime during admission‡ (%)	17 (4.6%)
Moderate ALT elevation anytime during admission‡ (%)	25 (6.8%)
Lymphocyte count (/l) at admission	1000 (100–5800)
IL-6 (pg/ml) at admission	37.5 (1.5–4079)
Ferritin (μg/l) at admission	518 (10–5503)
D-Dimer (μg/ml) at admission	252 (50–34144)
Lactate dehydrogenase (U/l) at admission	306 (139–1014)
HSI index	
<30 (%)	29 (7.8%)
30–36 (%)	102 (27.6%)
>36 (%)	169 (45.7%)

(continued)

Table 1. (continued)

Variable	*N* = 370
Missing (%)	70 (18.9%)
CAP (dB/m)§	252 (100–397)
>250 (dB/m)§ (%)	47 (48%)
>300 (dB/m)§ (%)	24 (25%)
LSM (kPa)§	4.7 (2.1–22.5)
>10 kPa§ (%)	2 (2%)
O_2 saturation with pulse-oximeter (%) at admission	97 (71–100)
Need for O_2 at admission (%)	147 (39.7%)
Need for FiO_2 > 30% at admission (%)	54 (14.6%)
Peak GGT (U/l) anytime during admission	83 (11–1691)
Peak AP (U/l) anytime during admission	91 (48–809)
Peak Bilirubin (mg/dl) anytime during admission	0.64 (0.20–5.20)
Lowest Albumin (g/dl) anytime during admission	3.3 (1.7–4.5)
Lowest platelet count (10E9/l) anytime during admission	202 (29–697)
Hospital length of stay (days)	7 (2–28)
ICU admission (%)	39 (10.5%)
Death (%)	17 (4.6%)
Death/ICU (%)	54 (14.6%)

Data are presented as median (range) or *n* (%).
ALT: alanine aminotransferase (elevated ALT > 35 U/l for women and >50 U/l for men); AST: aspartate transaminase (elevated ALT > 35 U/l for women and >50 U/l for men); AP: Alkaline phosphatase; BMI: body mass index; CAP: controlled attenuation parameter; GGT: gamma-glutamyl transferase; HSI: hepatic steatosis index; ICU: intensive care unit; IL-6: Interleucine-6; LSM: Liver Stiffness Measurement.
†Defined as >30 mg/d for men and 20 g/d for women.
‡Moderate AST/ALT elevations were defined as values >4× x upper limit of normal (i.e. 140 U/l for women and 200 U/l for men).
§Values correspond to 98 patients with elastography data.
ALT, alanine aminotransferase (elevated ALT > 35 U/l for women and >50 U/l for men); AP, alkaline phosphatase; AST, aspartate transaminase (elevated ALT > 35 U/l for women and >50 U/l for men); BMI, body mass index; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transferase; HIS, hepatic steatosis index; ICU, intensive care unit; IL-6, interleucine-6; LSM, liver stiffness measurement.

patient it was considered directly as COVID-19 related and the other was multifactorial during the ICU admission.

COVID-19 severity and outcomes

In terms of COVID-19 severity, 147 (39%) required oxygen support at admission, 54 (15%) of whom at a FiO_2 > 30%. During admission, 39 patients (10.5%) were transferred to the ICU and two of them died. Mortality at 28 days in the overall cohort was 4.6%, and during that 28-day interval, 54 patients (14.6%) experienced the composite endpoint ICU and/or death.

Table 2 shows the comparison in key characteristics according to occurrence or not of the main two outcomes. As expected, patients who died or experienced

Table 2. Main characteristics of patients and univariate comparisons according to main outcomes.

Variable	Death		*p*-value	Death/ICU		*p*-value
	Yes (*n* = 17)	No (*n* = 353)		Yes (*n* = 54)	No (*n* = 316)	
Male (%)	11 (64.7%)	170 (48.2%)	0.18	32 (59.3%)	149 (47.2%)	0.10
Age (years)	75 (70–80)	55 (46–65)	<0.0001	64 (53–72)	55 (45–65)	<0.0001
Origin			0.03			0.53
Europe (%)	14 (82.4%)	238 (67.4%)		40 (74.1%)	212 (67.1%)	
South America (%)	1 (5.9%)	101 (28.6%)		12 (22.2%)	90 (28.5%)	
Africa (%)	2 (11.8%)	8 (2.3%)		2 (3.7%)	8 (3.5%)	
Asia (%)	0	6 (1.7%)		0	6 (1.9%)	
Diabetes mellitus (%)	5 (29.4%)	53 (15.1%)	0.11	13 (24.1%)	45 (14.3%)	0.07
Hypertension (%)	11 (64.7%)	110 (31.3%)	0.004	27 (50%)	94 (29.8%)	0.004
Dyslipidemia (%)	6 (35.3%)	83 (23.6%)	0.27	15 (28.3%)	74 (23.5%)	0.45
BMI (kg/m^2)	29.6 (27.3–31.2)	28.6 (25.3–32.4)	0.58	29.6 (26.0–36.9)	28.5 825.3–32.3)	0.64
Obesity (%)	5 (38.5%)	124 (28.5%)	1.0	19 (40.4%)	110 (38.2%)	0.77
Previous liver disease (%)	1 (5.9%)	32 (9.1%)	0.65	4 (7.4%)	29 (9.2%)	0. 80
Cirrhosis (%)	1 (5.9%)	6 (1.7%)	0.28	2 (3.7%)	5 (1.6%)	0. 27
Risk Alcohol Consumption† (%)	0	16 (4.5%)	0.37	0	16 (5.1%)	0.14
ALT (U/L) at admission	39 (23–53)	31 (20–52)	0.57	35 (24–55)	30 (20–52)	0.18
ALT elevation at admission (%)	7 (41.2%)	123 (34.8%)	0.59	23 (42.6%)	107 (33.9%)	0.21
ALT elevated anytime during admission‡ (%)	11 (64.7%)	168 (47.6%)	0.17	26 (48.1%)†	135 (42.7%)†	0.46
Moderate ALT anytime during admission‡ (%)	1 (5.9%)	24 (6.8%)	1.0	4 (7.4%)†	9 (2.8%)†	0.11
AST (U/L) at admission	55 (38–83)	38 (29–54)	0.03	52 (36–73)	37 (29–52)	0.001
AST elevated at admission (%)	12 (70.6%)	155 (44.3%)	0.03	35 (64.8%)	132 (42.2%)	0.002
AST elevated anytime during admission‡ (%)	14 (82.4%)	197 (56.0%)	0.03	43 (79.6%)†	163 (51.7%)†	<0.0001
Moderate AST elevation anytime during admission‡ (%)	1 (5.9%)	16 (4.5%)	0.56	4 (7.4%)†	7 (2.2%)†	0.06
Lymphocyte (/L) at admission	600 (500–1250)	1100 (800–1500)	0.03	800 (600–1100)	1100 (800–1500)	<0.0001
IL-6 (pg/ml) at admission	96.7 (64.3–157.2)	36.8 (21.1–69.3)	<0.0001	75.8 (52.0–125.5)	33.6 (19.5–63.1)	<0.0001
Ferritin (µg/l) at admission	1055 (587–1574)	488 (253–834)	0.004	742 (488–1114)	450 (234–777)	<0.0001
D-Dimer (µg/ml) at admission	536 (269–1578)	246 (152–391)	0.003	335 (216–609)	243 (147–381)	0.003
Lactate dehydrogenase (U/l) at admission	512 (280–699)	305 (262–378)	0.01	384 (296–517)	300 (260–364)	<0.0001
HSI index at admission			0.38			

(continued)

Table 2. (continued)

Variable	Death		*p*-value	Death/ICU		*p*-value
	Yes (*n* = 17)	No (*n* = 353)		Yes (*n* = 54)	No (*n* = 316)	
<30 (%)	0	29 (10.1%)		4 (9.8%)	25 (9.7%)	0.99
30–36 (%)	6 (46.2%)	96 (33.4%)		14 (34.1%)	88 (34.0%)	
>36 (%)	7 (53.8%)	162 (56.4%)		23 (56.1%)	146 (56.4%)	
CAP (dB/m)§	-	249 (202–297)	-	226 (187–288)	249 (204–300)	0.45
CAP > 250 (dB/m)§ (%)	0	0	1.0	2 (40%)	44 (47.8%)	1.0
LSM (kPa)§		4.1 (3.5–5.1)		4.4 (3.8–5.0)	4.4 (3.5–5.2)	0.77
LSM > 10 kPa§	0	0	1.0	0	1 (1.1%)	1.0
Fever before admission (days)	5.5 (2.8–9)	7 (4–10)	0.26	7 (3–7)	7 (4–10)	0.06
Sat O_2 (%) at admission	92 (89–98)	97 (95–98)	0.005	95 (90–97)	97 (95–98)	<0.0001
Need for O_2 at admission (%)	13 (76.5%)	134 (38.0%)	0.002	40 (74.1%)	107 (33.9%)	<0.0001
Need for FiO_2 > 30% at admission	10 (58.8%)	44 (12.5%)	<0.0001	27 (50%)	27 (8.6%)	<0.0001
Hospital length of stay (days)	6 (4–12)	7 (5–12)	0.09	19 (9–28)	6 (5–9)	<0.0001

Data are presented as median (interquartile range) or *n* (%).
ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; HIS, hepatic steatosis index; ICU, intensive care unit; IL-6, interleukin-6; IQR, interquartile range; LSM: liver stiffness measurement.
†: defined as >30 g/day for men and 20 g/day for women.
‡Anytime before ICU admission (patients for whom AST elevated once at ICU were excluded for this calculations).
§Performed in 98 consecutive patients without oxygen support or with mild-moderate O_2 needs (Sa: FiO_2 > 300).

the composite endpoint were significantly older and were more frequently hypertensive; they also had lower baseline lymphocyte counts and higher ferritin, D-Dimer, and IL-6 values, showing the characteristic serum biomarker profile of severe COVID-19. Type-2 diabetes was associated with worse outcomes, both in univariate (Table 2) and multivariate analysis (Supplemental Table 4), although neither of these reached statistical significance. Obesity was not associated with either death or the composite endpoint.

The association between liver parameters and Covid-19 outcomes

Previous liver disease and transient elastography

The presence of pre-existing liver disease (including cirrhosis) was relatively uncommon (Table 1) in the whole cohort; therefore, significant differences in the main outcomes could be detected between patients with or without previous liver disease or cirrhosis (Table 2). Only one patient who developed decompensation after COVID-19 infection died.

Among the 98 patients undergoing TE, only 5 (5%) experienced the composite endpoint, and none of them died. As seen in Table 2, the median liver stiffness was similar between patients experiencing or not the composite endpoint.

Liver steatosis

Liver steatosis did not have any significant role in the outcomes of COVID-19 patients in our cohort. As seen in Table 2, when steatosis was addressed with the hepatic HSI, no differences in outcomes were detected at any HSI category. More specifically, patients with HSI > 36 had the exact same incidence of the composite endpoint as patients with HSI < 30 (no steatosis) or HSI 30–36 (Supplemental Table 1). In addition, the occurrence of death was similar between the three

categories. These outcomes did not change in those patients in whom the HSI could not be calculated because of missing parameters (Supplemental Table 1).

When steatosis was assessed with CAP in the 98-patient cohort, the results were similar. As seen in Table 2, the median CAP was not significantly different between patients experiencing or not the composite endpoint (no patients undergoing CAP measurements died). When stratifying using either a 250 dB/M or a 300 sB/M threshold, the incidence of the composite endpoint remained unchanged (Supplemental Table 1). When CAP was assessed as a continuous variable through logistic regression, no significant association with the composite endpoint was detected [OR 0.996, 95% confidence interval (CI) 0.981–1.010, $p = 0.551$].

ALT

As seen in Table 2, ALT elevations (analyzed either as continuous or dichotomous variables) were not associated with death at 28 days. When the association was analyzed through logistic regression (ALT elevations at admission or peak ALT at any time point during the episode, introduced as a continuous or dichotomous variable), the results remained unchanged (data not shown).

When applying the same analysis for the composite death and/or admission to ICU, elevated ALT at admission (either as continuous or dichotomous variable) was not associated with this outcome (Table 2 and logistic regression univariate analyses, data not shown). Both peak ALT (as a continuous variable considering the whole follow-up time: OR 1.011, 95% CI 1.007–1.015, $p < 0.001$) and elevated ALT at any time point during admission (as a dichotomous variable: 24%, 43/179 in patients with elevated ALT *versus* 5.8%, 11/191 in patients with normal ALT, $p < 0.001$) were significantly associated with the composite endpoint.

However, among the 54 patients experiencing this outcome, the ALT elevation occurred after the patient was admitted to the ICU in 36% (15/41) of the cases. Indeed, if ALT elevations happening after admission to the ICU were excluded from the analysis (i.e. only ALT values before ICU admission were considered), the association of ALT elevations with the composite endpoint death/ICU disappeared (OR 1.245, 95% CI 0.698–2.220, $p = 0.46$; 16.1%, 26/161 in patients with elevated ALT at any time before ICU admission *versus* 13.4%, 28/209 in patients with normal ALT, $p = 0.46$).

AST

On the other hand, AST elevations were strongly associated with outcomes in our cohort. As shown in Table 2, median AST (either at admission or at any time point during admission) was significantly higher in patients who died or reached the composite endpoint. In addition, when compared with patients with normal AST values at admission, those with abnormal baseline AST had a significantly higher occurrence of death (7.2% *versus* 2.5%, respectively, $p = 0.03$) and the composite ICU/death endpoint (21% *versus* 9.5%, $p = 0.002$) (Supplemental Table 2). All these differences remained significant, even after exclusion of patients with previously known liver disease (data not shown) or with AST elevations occurring once admitted to the ICU (Table 2). Moderate AST elevations, either at admission or before ICU, were uncommon ($N = 7$ and 11, respectively) and did not affect outcomes substantially (differences in outcomes remained unchanged after excluding these patients, data not shown).

In order to adjust the weight of AST by other well-known risk factors on COVID-19 outcomes, two approaches were taken.

Firstly, an exploratory adjustment using logistic regression analysis was performed (see Methods for details). Age and O_2 saturation at admission were maintained as the main covariates for adjustment. As seen in Table 3, both the OR and *p*-value of AST remained unchanged after adjustment with those two clinical variables. To further adjust the weight of AST with other blood prognostic markers available at admission, several combinations of these biomarkers were studied. Lymphocyte count and DD showed as the two more stable and consistent variables, and thus were used to further adjust OR estimates for AST on the composite endpoint. As seen in Supplemental Table 3, AST lost stability when introduced with those two variables, most likely due to the loss of linearity and discriminative ability for normal values. However, AST remained highly significant when kept as a dichotomous variable. When the age-O_2-AST block was

Table 3. Logistic regression adjustment of the weight of AST on the composite endpoint death and/or ICU.

	Univariate models		Multivariable models			
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
AST (U/l)	1.007 (1.001–1.013)	0.03	1.007 (1.001–1.014)	0.02	1.007 (1.001–1.014)	0.02
Age (years)	1.041 (1.021–1.069)	<0.001	1.042 (1.019–1.066)	<0.001	1.031 (1.006–1.056)	0.01
O_2 saturation (pulse-oximeter) (%)	0.882 (0.832–0.936)	<0.001			0.906 (0.850–0.964)	0.002

AST, aspartate aminotransferase; CI, confidence interval; ICU, intensive care unit; OR, odd's ratio.

adjusted by the presence of hypertension, the latter was not found to remain significantly associated with the composite endpoint (see Supplemental Table 3).

Secondly, CART analysis was used to explore relevant, non-parametric interactions between all these pre-selected variables and to obtain discriminative cut-off values for continuous variables. Age was forced as first node based on the reasons stated above (clinical relevance, available literature, and potential utility for rapid triage at all healthcare levels). Interestingly, an AST value at admission of 50 U/l was identified as the most discriminative and stable parameter to identify a high-risk population in the cohort (Figure 1).

As seen here, patients of age 65 or older had a 2.5 increase in risk of the composite endpoint when compared with patients below that age threshold (26/107, 24.3% *versus* 28/263 10.6%, respectively, $p=0.001$). In that population of 65 or older, patients with AST $\leqslant$ 50 U/l at admission had a similar risk to that of patients <65 (10/75, 13.3%), while 50% (16/32) of these older patients with AST >50 U/l either were admitted to the ICU and/or died, a risk almost 5 times higher than for the other categories ($p<0.001$).

Finally, given the lack of association between ALT, TE, and pre-existing liver disease with outcomes, the association between AST and LDH was further explored, under the hypothesis that both elevations could be consequence of muscular micro-damage [creatinine phosphokinase (CPK), aldolase, and other muscular enzymes were not routinely available through the study period) and thus linked in terms of predictive ability. As seen in Supplemental Figure 1, there was a modest but significant linear correlation between AST and LDH at admission.

Interestingly, when both parameters were plotted highlighting the occurrence or not of the primary endpoint, it could be observed that LDH elevations without AST increase were very common, but remained poorly predictive of the outcome, suggesting a higher discriminative hierarchy of AST over LDH. AST and ALT were highly correlated both at admission and when comparing peak values for each patient during the whole episode (R square 0.743, $p<0.001$ and 0.630, $p<0.001$, respectively).

Discussion

In this prospective observational study in a large cohort of consecutive patients admitted for COVID-19, we used a comprehensive diagnostic approach (using clinical variables, blood tests, and TE) to evaluate the hepatic involvement of liver disease in COVID-19 outcomes. In contrast to previous reports, we did not find any significant association of either previous liver disease, liver steatosis or ALT elevations with hard clinical outcomes; however, this study was not powered for this.[5–10,14,15] We observed a strong association between baseline AST values an outcomes, especially in older patients.

One of the main results in our study is that, in contrast to previous reports by other groups,[8–10] we did not find any association between liver steatosis and worse outcomes in COVID-19. The evaluation of steatosis in previous reports has been made based either on indirect serum scores based on transaminase ratios (such as HSI) ultrasound, or CT scan, which have suboptimal

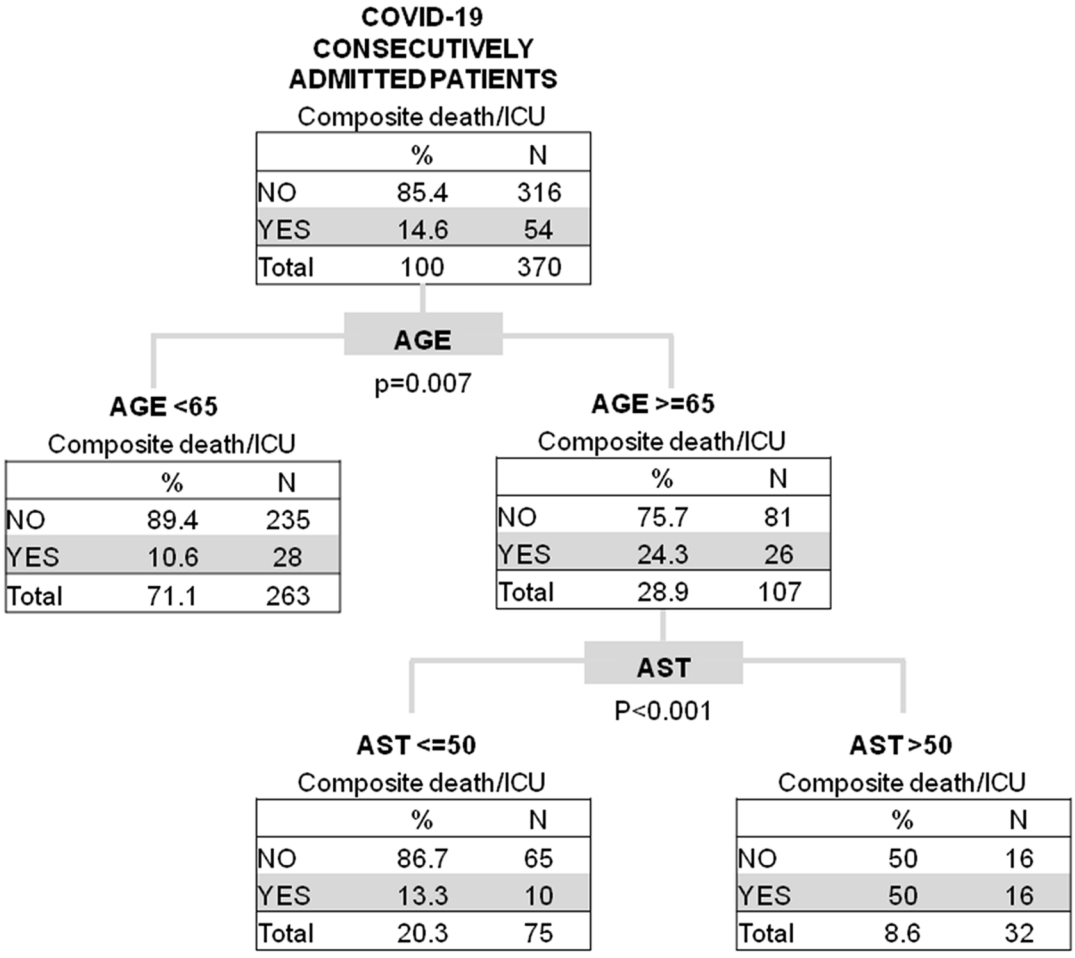

Figure 1. Classification and Regression Tree (CART) analysis of covariates associated to the composite endpoint death and/or ICU in the cohort.
ALT, alanine aminotransferase; AST, aspartate transaminase; ICU, intensive care unit.

sensitivity for steatosis detection.[17] To the best of our knowledge, this is the first report on the use of TE to evaluate the involvement and predictive value of liver disease in patients with COVID-19. Fibroscan CAP is widely used for steatosis quantification and was evaluated in the present study as an early prognostic tool in 98 consecutively admitted patients with mild-to-moderate COVID-19. In this sub-cohort, patients, with-or-without steatosis, had the exact same incidence of the composite endpoint death/ICU, and comparison of the CAP value distribution in the two groups did not differ. In addition, we used HSI (using only values at admission) to further study the association in the whole cohort of 370 patients, with similar results. The reasons for this discrepancy with previous reports are not clear. As referred above, CAP is more sensitive than other tools to detect steatosis; therefore, the latter technique might be selecting a higher-risk population. In our view, this reason is unlikely given, on the one hand, the very low frequency of events even in patients with higher CAP values; on the other hand, the lack of association in our cohort between obesity or diabetes (which are generally associated with a higher degree of steatosis) with outcomes. Regarding HSI, previous reports used varied timeframes to select the values entered in the calculation of the score, which may justify to some degree the difference in results. In any case, given the characteristic changes of ALT and AST in patients with COVID-19, the transferability of the diagnostic accuracy for steatosis or fibrosis of transaminase-based scores derived from chronic liver disease to this peculiar setting (in which ALT/AST dynamics seem to be different to that

from chronic liver disease) should be put into question.

Our study was not able to confirm previous studies that suggest that prior liver disease had an effect on COVID-19.[7,22] However, the present study is not suited to tackle this question, given the limited number of patients with previous liver disease in our cohort. This question should be addressed through large registry-based studies, ideally including adequate control groups.

Nonetheless, the present study provides clinically relevant data on the association of ALT elevations in patients with COVID-19. Liver injury (assessed with different transaminase-based criteria) and its relationship with COVID-19 have been evaluated in several studies, with conflicting conclusions.[5,6,11,12,14,15,23–25] In our large, prospectively collected cohort, we did not observe a significant association between baseline ALT elevations and outcomes. In addition, both moderate ALT elevations and acute hepatitis were rare and occurred mostly in patients already at the ICU. The only associations between ALT and outcomes observed in our cohort were mostly due to the occurrence of ALT elevations once the patient was admitted to the ICU, defeating the purpose of using ALT elevations as predictor of hard clinical outcomes. Our results suggest that most often it is ICU admission that anticipates ALT elevations, rather than *vice versa*, pointing out at an adequate analysis of timing of ALT elevations as of critical relevance in order to provide a correct interpretation of causality.[23]

Finally, the most relevant result of our study was the observation of the association of AST elevations with worse COVID-19 outcomes. In our cohort, patients with abnormal AST at admission had twice the risk of death/ICU admission than those with normal values. AST remained as a strong predictor of the composite endpoint, even after adjustment with other key clinical variables like age or O_2 saturation at admission. In this regard, AST was only discriminative in older patients. In patients younger than 65, AST elevations did not seem to associate with worse outcomes. However, in patients older than 65, an AST value at admission above 50 allowed the identification of a high-risk population with a 50% risk of evolving to either ICU admission or death.

Given the lack of association between ALT elevation an outcomes, the origin of AST in these patients remains as an intriguing question. In a recent paper, Bloom *et al.*[12] observed a strong correlation between ALT and AST elevations (with no predictive effect on neither ICU admission nor death) and based on these data the authors suggested an effect of direct hepatic injury on COVID-19. Our results suggest otherwise. Despite the linear correlation between AST and ALT in our study, there was a distinct effect of each transaminase on outcomes. The difference in sample size (370 *versus* 60) and follow-up time (28 *versus* 14 days) between both studies may account for some of these differences, but a reasonable alternative is assuming a different origin for AST elevations in COVID-19. Since other viral hepatitis are led by ALT elevations and many viral diseases associate different degrees of muscular damage, the predominant AST elevation observed in COVID-19 has been suggested to be related to muscular micro-damage. We found a modest correlation between AST and LDH at admission, but the discriminative ability of AST is definitively higher than that of LDH. The results by Bloom and colleagues suggest that the correlation between AST and muscular enzymes is low in these patients.[12] Therefore, further studies are needed to clarify whether the different meaning of AST elevation in COVID-19 is due to a particular form of liver damage (independent of ALT elevations) or to micro-damage in other tissues.

Our study has some limitations. Firstly, elastography was only performed in a subset of patients and results cannot be extrapolated to the whole population. The initial aim of TE evaluation was to study its role as a prognostic tool; therefore, the focus is on less sick patients. For this aim, TE does not seem useful, but at least it allows for the observation of a lack of association between steatosis (as defined both by CAP and HSI), which remains valid.

Secondly, the low number of patients with previous liver disease preclude us from evaluating its impact on COVID-19 outcomes, as described above. However, it is possible that within the cohort there were patients with chronic liver disease (NASH, alcohol-related) not previously identified. Another limitation was that we did not account for the use of drugs during admission or

ICU stay; however, as the main focus and results of the present study are baseline variables, we believe this limitation can be neglected.

Finally, this study was not aimed at developing comprehensive prognostic tools, but rather to study the role of liver parameters on hard outcomes. The correlation of AST with other relevant prognostic markers of COVID-19 outcomes could be further developed, but it was out of the scope of the present work, which was centered on the liver involvement in COVID-19. Nonetheless, we think that the potential utility of AST as a prognostic marker in COVID-19 should be further studied, given its simplicity and wide availability.

Despite these limitations, the study has clear strengths. This is the largest cohort reported to date focusing on the role of liver biochemistry and steatosis on COVID-19 outcomes, and the first one to study steatosis adequately. The study was prospective, with data collected in almost real time, limiting the loss of information. Finally, one of the main strengths of the present study is the long follow-up of patients and its focus on hard clinical outcomes, which make the observed associations significantly more robust and relevant to clinical practice.

In conclusion, mild liver damage is very prevalent in COVID-19 patients, but neither the presence of ALT elevations nor prior hepatic steatosis carry worse outcomes. Elevated AST at admission is a strong predictor of hard clinical outcomes, especially in patients older than 65 years.

Author contributions

Study concept and design: IC-V, SA, JG. Patient enrollment and acquisition of data: AV, MS-T, MR-B, MV-C, LA-C, PA-L, EA, AA, JB, CB, AB-D, BB, LC, AC, RC, CD, AF, CJ, MJ, CG, CG-G, DG, JAG, BL, CM, JM-C, LM, EM, MMJ, EP, AP, MP, AP, JR, AR, ST, JV-G, LV, BM. Analysis and interpretation of data: SA, IC-V. Drafting of the manuscript: IC-V, SA, JG. Critical revision of the manuscript: AV, MS-T, MR-B, MV-C, LA-C, PA-L, EA, AA, JB, CB, AB-D, BB, LC, AC, RC, CD, AF, CJ, MJ, CG, CG-G, DG, JAG, BL, CM, JM-C, LM, EM, MMJ, EP, AP, MP, AP, JR, AR, ST, JV-G, LV, BM. All the authors approved the final draft which is being submitted.

Conflict of interest statement

IC-V: Travel and conference grant from MSD, Astellas and Chiesi. SA: consulting fees from Boehringer Ingelheim, Ferrer, Gilead, Intercept, IQVIA, Novartis, Pfizer; speaking fees from Allergan, Gilead, MSD and Novartis; travel expenses from Gilead, MSD, Janssen, Genfit, Bayer and Ferring; grant support from Gilead.

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Supplemental material

Supplemental material for this article is available online.

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