RESEARCH ARTICLE

Role of transaminases, CRP and LDH in COVID-19 patients with and without respiratory failure during the disease outbreak

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TRANSPARENCY DECLARATION
The lead author Bianca Magro affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ETHICAL APPROVAL: The study was approved by the local Ethical Committee (Reg. Sperim. 37/20).

ABSTRACT

BACKGROUND: Sars-Cov-2 pneumonia is a pandemic disease with high morbidity and mortality. In literature transaminases, CRP and LDH were frequently found abnormal but their role has not been clarified.

OBJECTIVES: Aim of this retrospective study is to explore the role of transaminases, CRP and LDH on short-term prognosis of hospitalized COVID-19 patients.

METHODS: patients admitted in hospital for COVID-19 were consecutively recruited. Primary endpoint: evaluate role of transaminases, CRP and LDH on disease progression (DP). Secondary endpoints: find possible risk factors for (1) mortality and (2) CPAP ventilation at day 7. We also analyzed patients without respiratory failure at admission, also a subgroup of patients with liver disease.

RESULTS: 342 patients were included. Median age of patients was 64 years (IQR 55-74), and 35.1% (n=120) was female. At multivariate analysis moderate ALT elevation at Day 1 (p=0.001, OR 2,42, CI95% 1.23-4,73) and CRP at Day 7 (p=0.001, OR 1, CI95% 1-1,1) were predictors of DP; LDH at admission (p=0.05, OR 1, CI95% 1.23-1,1) and moderate AST elevation at day 7 (p=0.04, OR 4,5, CI95% 1.05-19,4) were predictors of CPAP at day 7. At multivariate analysis age (p<0,001, OR 1,12, CI95% 1-1,2) and sex (p=0.01, OR 14, CI95% 1,7-116,7) were predictors of death. Mortality rate of patients with liver disease was 25%(n=3/12).

CONCLUSIONS: Moderate ALT elevation at day 1 and moderate AST elevation at day 7 were respectively, predictors of DP and CPAP at day 7. For patients without respiratory failure, transaminases are not significative for anyone of our outcomes. Age, sex and CRP at day 1 are death risk factors.

Keywords: *Coronavirus; COVID-19; risk factors; prognosis; mortality; italy; pandemic*

INTRODUCTION

In December 2019, first cases of coronavirus disease (Covid-19) were identified in the Chinese region of Wuhan. This virus is a novel enveloped RNA beta-coronavirus, and it can lead to severe acute respiratory syndrome (SARS -CoV-2)[1–5].

On 11th march 2020 Covid-19 has been declared pandemic by World Health Organization (WHO), having infected more than 100.000 people in the world.

In a variable percentage of patients, alterations in C-reactive protein (CRP), lactate dehydrogenase (LDH) and transaminases (both alanine aminotransferase- ALT, and aspartate aminotransferase-AST) values, were shown, however only scattered data have been published to date aiming at establishing a possible role in predicting the clinical course[1].

One other report from China[6], focused on liver injury in Covid-19, seven case series showed that 2-11% of patients had liver comorbidities and 14-53% reported abnormal ALT and AST serum values during disease. A study by Huang and colleagues[7] showed that AST elevation was higher in ICU patients (62%) compared with those who did not require ICU. The vast majority of the reported studies are from Far East countries[1,7–11], where COVID-19 has spread at first, and only scattered data are available from Western countries[12,13]. In Italy, the first documented case of Coronavirus infection was on February 21st and in one month an exponential growth in contagions and deaths has been observed, reaching

respectively over 90.000 documented cases and over 10.000 demises[14,15]. One of the cities epicenters of epidemic COVID-19 in Italy was Bergamo, and its hospital is one of the centers with most admitted infected patients[16].

Aim of this retrospective study is to explore the possible clinical role of transaminases and CRP in defining the prognosis of hospitalized COVID-19 patients, both with liver disease and not.

METHODS

Patients

We retrospectively analyzed 343 consecutive patients admitted at HPG23 for COVID-19 infection, in the period of time ranging from February 22th and March 30th 2020

Inclusion criteria were: age > 18 years; a Sars-Cov-2 nasal swab positive.

We focused on all those lab tests that were routinely performed at the Emergency Department that are often increased in these patients (transaminases, CRP and LDH)

Exclusion criteria were: outpatients with no need of hospital admission, patients requiring ventilatory support in ICU at admission, patients without information on the clinical course at 7 days.

We considered two subgroups according with the presence or the absence of respiratory failure ad admission.

We also identified patients with liver disease and we analyzed clinical and laboratory findings.

Liver disease was defined by medical history of chronic liver disease

Respiratory failure was defined by the presence of any of the following conditions: i) significantly increased respiration rate (RR): RR > 30 times/minute; ii) hypoxia: oxygen saturation (resting state) <−93%; iii) blood gas analysis: partial pressure of oxygen/fraction of inspired oxygen (PaO2) /FiO2) < 300 mmHg (millimeters of Mercury). [17]

Cardiopathy was defined as medical history of coronary artery disease.

Data collection

Medical history, clinical symptoms and laboratory findings were extracted from electronic medical records at the moment of the hospitalization and at day 7. The paper was written according to STROBE recommendations (Supplementary Table 1)[18].

Outcome

Primary endpoint was to evaluate the role of transaminases, CRP and LDH at admission and after one week on disease progression. We defined disease progression as the worsening in ventilation support after seven days from hospitalization.

The secondary endpoints were to evaluate possible risk factors for: (1) mortality and (2) need of CPAP (Continuous Positive Airway Pressure) at day 7.

We divided transaminases elevation in mild (< 2 UNR) and moderate (> 2 UNR), according to American College of Gastroenterology definition [19]

LDH, CRP were defined significantly increased or decreased if there was an a ± 50% difference in the absolute value at day 7 compared with the admission value.

The onset of clinical history, comorbidities and treatments were recorded. Laboratory tests consisted of a complete blood count, creatinine, c-reactive protein, lactate dehydrogenase, assessment of liver function, electrolytes.

We searched for possible predictors of disease progression at univariate analysis considering the subsequent variables: age, sex, liver disease, symptoms of presentation (fever, respiratory, neurological, gastrointestinal ones), LDH/AST/ALT/CRP values at admission and after 7 days, comorbidities (arterial hypertension, cardiopathies, rheumatological/neurological/nephrological/respiratory ones, obesity, use of ARBs).

Statistical analysis:

Data for continuous variables are presented as mean and standard deviation (SD) or as median and interquartile range, and data for categorical variables as frequency and percentage. Differences between continuous data were analyzed by Student t test and Chi square test

was used for dichotomous or categorical variables. The univariate and multivariate logistic and linear regression model were used to assess the independent factors of disease progression. Variables with a p value < 0.1 at univariate analysis were included in the multivariate model. A p-value < 0.05 was considered statistically significant. Statistical analysis was conducted using MedCalc Statistical Software Version 12.5.0 (MedCalc Software LTD, Ostend, Belgium).

RESULTS

Baseline characteristics

Baseline characteristics of the 342 patients are reported in Table 1 according to the presence (n=135) or the absence (n=207) of respiratory failure at admission.

Table 1: Baseline features of patients according to the presence of respiratory failure at admission

	Total (n=342)	***Respiratory failure (n=135)***	***No Respiratory failure (n=207)***
Age median	64 (55-74)	68 (58,25- 74)	63 (51-74)
Female n (%)	120 (35,1)	24 (33,3)	75 (36,2)
Liver disease (LD) n (%)	12 (3.5)	9 (6.7)	3 (1.5)
Hypertension n (%)	152 (44.7)	64 (47.4)	88 (42.9)
Diabetes n (%)	47 (13.8)	25 (18.5)	25 (12.2)
Obesity n (%)	36 (11.8)	10 (7.4)	26 (15.2)
Fever n (%)	288 (84.5)	129 (95.6)	159 (77.6)
Gastrointestinal symptoms n (%)	41 (12)	17 (12.6)	24 (11.7)
Respiratory symptoms n (%)	187 (54.8)	126 (93.3)	61 (29.6)
Neurological symptoms n (%)	10 (2.9)	10 (7.4)	0
Cardiological comorbidities n (%)	47 (13)	28 (20.7)	19 (9.3)
Oncological comorbidities n (%)	20 (5.9)	7 (5.2)	13 (6.3)
Pneumological comorbidities n (%)	25 (7.4)	14 (10.4)	11 (5.4)
Nephrological comorbidities n (%)	21 (6.2)	4 (3)	17 (8.3)
Reumathological comorbidities n (%)	10 (2.9)	3 (2.2)	7 (3.4)

Median age of patients was 64 years (IQR 55-74), and 35.1% (n=120) was female.

The most common symptoms were respiratory ones (54,8%; n=187).

In the cohort of patients without respiratory failure at admission median age was 63 (IQR 51-74), and 36,2 % was female. The most common symptom was fever (77,2%, n=159).

Among comorbidities the most represented was hypertension (44,7%; n=152) followed by diabetes (13,8%; n=47).

The 17.2% of the population was in treatment with Angiotensin Receptor Blockers (ARBs) and/or Angiotensin Converting Enzyme inhibitors (ACE-inhibitors).

All patients were treated with lopinavir–ritonavir (400 mg and 100 mg, orally twice daily) and Hydroxychloroquine (200 mg, orally twice daily), that was the only treatment available during the disease outbreak.

Laboratory findings

Data on transaminases, CRP and LDH are shown in Supplementary table 2.

Median value at Day 1 of serum AST and ALT were respectively 41 U/L (IQR 26-63,25) and 34 U/L (IQR 23-58) and they were above the upper normal range in 50.6% (n=163) and 40.7% (n=129) of cases. After one week of hospitalization AST and ALT median values were respectively 40 U/L (IQR 25-62) and 42,5 U/L (IQR 26-71). The difference between ALT at day 1 and at day 7 was statistically significant (p=0.002)

Moreover, in the subgroups of patients with and without respiratory failure we found statistically significant differences in CRP (p<0.001), AST (p<0.001), ALT (p=0.03) and LDH (p<0.001) at admission, and in CRP (p=0.02), AST (p=0.001) and LDH (p<0.001) at day 7.

Classifying patients according with transaminases values, we found that mild and moderate ALT elevation was present respectively in 35,9% (n=105) and 18,2% (n=53) of cases. Similarly, mild and moderate AST elevation was observed in 33,4% (n=97) and 14,5% (n=42) of patients. In 41,9% (n=133) patients' transaminases were both normal, while the moderate elevation of both AST and ALT values was present in 9,1% of patients (n=29).

Mild and moderate AST and ALT elevation were reported in Supplementary table 3 according to the presence of respiratory failure.

CRP median value at day 1 was 7 mg/dl (2-14) and at day 7 15 mg/dl (5-27,25)

LDH median value at day 1 was 329 (260,5-463) and at day 7 302 U/L (242-400)

Patients with liver disease

Among the patients included in our study, 3.5% (n=12/342) were affected by a liver disease: 3 chronic viral hepatitis, 4 cirrhosis alcohol related, 5 nonalcoholic fatty liver disease/ nonalcoholic steatohepatitis. Median age was 64 years (IQR 56-74) and 16.7% (n=2/12) were female. Features are shown in Supplementary Table 4. At admission 3 patients did not need oxygen ventilation, 5 patients were on nasal cannulas/Venturi Mask (41.7%) and 4 patients were on reservoir mask (33.3%).

Median value at hospital admission of serum AST and ALT were respectively 45 U/L (IQR 27-63.5) and 33 U/L (IQR 24-54). Mortality rate was 25% (n=3/12).

Disease progression

Pulmonary disease progression was observed in 133/342 patients (38.9%) with an increased need in ventilation support: one hundred fourteen patients needed to begin oxygen ventilation (81 patients to nasal cannula/Venturi mask, 11 to Reservoir mask and 22 to CPAP), 17 from nasal cannula/Venturi mask (15 to Reservoir mask and 2 to CPAP) and 2 from Reservoir mask to CPAP.

The variables resulted significative at univariate analysis for DP were sex, ALT at day 1 > 2 UNR; CRP value at day 7 and respiratory failure at admission.

In the subgroup analysis of patients without respiratory failure the significative variables at univariate analysis were: sex, fever, LDH at day7, moderate ALT elevation at day 1, CRP value at day 1 and at day 7

At multivariate analysis moderate ALT elevation at Day 1 (p=0.001, OR 2,42, CI95% 1.23-4,73) and CRP at Day 7 (p=0.001, OR 1, CI95% 1-1,1) were predictors of disease progression. (Table 2)

We also analyzed patients without respiratory failure and at multivariate analysis LDH at Day 7 was the only predictor of DP (p=0.01, OR 1, CI95% 1-1,1)

CPAP at day 7

During the course of hospitalization 27/342 (7.9%) patients needed CPAP.

Possible predictors for CPAP, at univariate analysis, were LDH, AST at day 7> 2 UNR, CRP at day 7, while for patients without respiratory failure LDH, CRP at day 7 and respiratory symptoms at admission were significative

We analyzed in multivariate analysis predictors of CPAP. (Table 2) (Table 3)

In the first group LDH at admission (p=0.05, OR 1, CI95% 1.23-1,1) and moderate AST elevation at day 7 (p=0.04, OR 4,5, CI95% 1.05-19,4) were predictors. (Table 2)

In the second group respiratory symptoms at admission (p=0.02, OR 6,62, CI95% 1.44-30,27), and LDH at Day 7 (p=0,01, OR 1,1, CI95% 1-1,1 and CRP at day 7 (p=0.05, OR 1,1, CI95% 0,9-1) were significative

Table 2: Multivariate analysis for DP, death and CPAP at day 7 in the entire cohort of patients

	Variable	***P (univariate analysis)***	***P (multivariate analysis)***	***Odds ratio (CI95%)***
Disease Progression	Sex	0.045	0,28	
	ALT at day 1 > 2UNR	0.01	**0,01**	***2,42 (1,23-4,73)***
	CRP at day 7	<0.001	**0,007**	***1,1 (1-1,1)***
Death	**Age**	<0.001	**<0.001**	***1,1(1,01-1,2)***
	Sex	0.003	**0.01**	***14,22 (1,7-116,73)***
	LDH at day 1	<0.001	0.12	
	AST at day 1 > 2 UNR	0.02	0.23	
	Nephrological comorbidities	0.02	0.22	
	Cardiological comorbidities	<0.001	0.10	
	Pneumological comorbidities	0.02	0.69	
	Treatment with sartans	0.04	0,19	
	CRP at day 1	<0.001	0.01	
CPAP at day 7	**LDH at day 7**	<0.001	**0,002**	***1,1 (1-1,1)***
	CRP at day 7	<0.001	**<0.001**	***1.07 (1.01-1.1)***
	AST at day 7 > 2 UNR	0.01	0,09	

Table 3: Multivariate analysis for DP, death and CPAP at day 7 in the subgroup of patients without respiratory failure

	Total (n=342)	***Respiratory failure (n=135)***	***No Respiratory failure (n=207)***
Age median	64 (55-74)	68 (58,25- 74)	63 (51-74)
Female n (%)	120 (35,1)	24 (33,3)	75 (36,2)
Liver disease (LD) n (%)	12 (3.5)	9 (6.7)	3 (1.5)
Hypertension n (%)	152 (44.7)	64 (47.4)	88 (42.9)
Diabetes n (%)	47 (13.8)	25 (18.5)	25 (12.2)
Obesity n (%)	36 (11.8)	10 (7.4)	26 (15.2)
Fever n (%)	288 (84.5)	129 (95.6)	159 (77.6)
Gastrointestinal symptoms n (%)	41 (12)	17 (12.6)	24 (11.7)
Respiratory symptoms n (%)	187 (54.8)	126 (93.3)	61 (29.6)
Neurological symptoms n (%)	10 (2.9)	10 (7.4)	0
Cardiological comorbidities n (%)	47 (13)	28 (20.7)	19 (9.3)
Oncological comorbidities n (%)	20 (5.9)	7 (5.2)	13 (6.3)
Pneumological comorbidities n (%)	25 (7.4)	14 (10.4)	11 (5.4)
Nephrological comorbidities n (%)	21 (6.2)	4 (3)	17 (8.3)
Reumathological comorbidities n (%)	10 (2.9)	3 (2.2)	7 (3.4)

Death

In our cohort death events within the first 7 days were observed in 14.9% (n= 51) of the cases, 43 males (84.3%) and 8 females (10%, p=0.002). Median age of the patients who died was 75 years (IQR 70 - 82).

At multivariate analysis age (p<0,001, OR 1,12, CI95% 1-1,2) and sex (p=0.01, OR 14, CI95% 1,7-116,7) (Table 2) were predictors of death.

In the subgroup of patients without respiratory failure age (p<0,003, OR 1,14 CI95% 1-1,22) and CRP at day 1 (p=0,01, OR 1,1, CI95% 1-1,2) were significative.

DISCUSSION

The rapid spread of the Covid-19 infection and the rapidity of respiratory deterioration hamper the possibility to meet the needs of many critically ill patients, simultaneously presenting in the Emergency Department [20,21].

Our study was specifically oriented on the identification of potential risk factors of disease progression or death, with a particular focus on transaminases serum levels. Another goal was

to compare the two subgroups of admitted Covid-19 patients, with and without respiratory failure. In literature some studies considering the possible role of transaminases elevation in Covid-19 infection have been reported [22,23,2425]

All these studies are burdened by some biases as the fact that in most cases patients were selected according to the gravity of their disease or that transaminases values were not adjusted for other possible competitive factors.

As described in study conducted in China[1], which reported serum transaminases elevation rate of 14–53%, we also found that AST and ALT were abnormal in approximatively half of patients (respectively 50.8% and 54.1%) . In this Chinese study, it is also reported a higher rate of abnormal transaminases in ICU patients, with an increasing trend during hospitalization.

Another important recent study of more than 5000 patients showed that AST increase, especially in severe patients, was associated with the highest mortality risk.[26]

We differentiated patients according to the grade of transaminases elevation, AST and ALT moderate elevation at day 1 and at day 7 were respectively 15,6% -18,2% and 14,5% - 23,1%. Moreover, we also analyzed patients according to the presence of respiratory failure at admission.

In our analysis we found at multivariate analysis that moderate AST elevation at day 7 is a predictor of CPAP ventilation for patients with respiratory failure at admission (p=0,04, OR 4,52)

Also, in a large cohort of COVID-19 patients (n=551), AST elevation was associated with higher mortality, in this case authors suggested as possible etiology the ischemic injury. [27]

Wang et al in their study reported that a possible factor for the liver injury occurrence in Covid-19 patients could be the high levels of positive end expiratory pressure that can cause hepatic congestion by increasing right atrial pressure and impeding venous return.[28]

Moreover, we individuated as predictor of DP, at multivariate analysis, moderate ALT elevation at day 1 (p=0,001 OR 2,43).

Regarding patients without respiratory failure at admission transaminases elevation at day 1 and/or at day 7 was not a predictor for anyone of the outcomes considered in our study.

If we consider Sars-Cov-2 pneumonia as a trigger for a huge inflammatory response, we can suppose that in patients with a more severe disease (respiratory failure at admission) transaminases elevation could be considered as a surrogate of a more severe systemic disease, but with the limited availability of clinical and laboratory data it is difficult to be conclusive.

All patients hospitalized in our hospital, during the “first wave” of the pandemic, were in treatment with ritonavir/lopinavir from day to of hospitalization, in this case drug induced liver injury (DILI) is not likely for the occurrence time of hypertransaminasemia, but for the certain diagnosis hepatic biopsy was necessary.

Another possible cause of transaminases elevation could be related also to the viral infection of cholangiocytes through ACE2[29] or to the systemic inflammatory cytokine storm that could involve liver too.[30,31] Furthermore, in the small subgroup of patients with a baseline liver disease, transaminases and CRP values were not significantly different respect to general population.

Regarding patients with pre-existing liver disease, we found the 3.5% affected by LD. In this recent meta-analysis prevalence of liver disease in Covid-19 patients was very low (3%), but it was conducted on 2034 patients, the most common cause was viral chronic hepatitis (HCV or HBV).[32] In our findings pre-existing liver disease was not found to be a predictive factor for mortality and disease progression, but we should not consider these results as conclusive because of the small sample size.

From our data, to underline role of the inflammatory response, CRP at day 7 emerged as predictor of DP (p=0,001 OR 1,1) and it was also a predictor for CPAP ventilation at day 7 (p=0,05 OR 1,1) in the subgroup of patients without respiratory failure at multivariate analysis.

Also, in another recent study CRP and transaminases emerged as risk factors of mortality in COVID-19 hospitalized patients. [33]

Since CRP is elevated in most inflammatory conditions, so as pneumonia[34], its prognostic role need to be carefully weighted. Indeed, with such awareness, regular monitoring of CRP values during hospitalization should be carried out in relation to clinical features.

Other studies put their attention on LDH as possible risk factor of more severe disease [35]

Our data showed that LDH at day 7 is predictor of DP and CPAP ventilation for patients without respiratory failure (p=0,01; OR 1,1-p=0,001; OR1), while LDH at day 1 is a predictor of CPAP for patients presenting respiratory failure at admission (p=0,05; OR 1). LDH is released from cells upon damage of cytoplasmic membrane and its levels might reflect tissue necrosis related to immune hyperactivity, which thus relates to poor outcome [36]

While focusing on death, mortality rate (14,9%) was higher compared to other studies from the Far East (3%), likely due to differences in the study populations: not only our population was older but, once more, outpatients were not included in our series.

At multivariate analysis we found age (p<0,001 OR 1,12) and sex (p=0,01 OR 14,22) as predictors, while for patients without respiratory failure age (p=0,001 OR 1,13) and CRP at day 1 (p=0,01 OR 1,14) were significative

In the literature gender had already been studied in Covid-19 patients, showing the same mortality but a less severe disease in females. In fact, sex hormones can affect the inflammatory modulation during infection, with estrogens promoting both innate and adaptive immunity having a suppressive effect on immune function [37,38,]

No differences were found in outcomes after excluding patients with pre-existing liver disease.

This study presents some intrinsic limits such as the relatively small sample size, the retrospective design and the short initial duration of patient observation. Especially regarding this last point, a seven days observation, can define the short-term outcome, but may underestimate both long term disease progression and mortality. In view of the rapid deterioration of respiratory function, the large number of infected patients and the limited available data that we can use to manage this pandemic disease, these data suggest which could be biochemical and clinical variables to consider during the hospitalization of Covid-19 patients with pneumonia. Therefore, our study can only be referred as the picture of mortality rate among hospitalized patients with COVID-19 in Italy.

CONCLUSIONS

In conclusion we identified possible risk factors of a more severe disease, especially we found that almost all patients had a mild transaminases alteration, but it is the moderate ALT elevation at day 1 and the moderate AST elevation at day 7 respectively, predictors of DP and CPAP at day 7.

Moreover, for patients without respiratory failure, transaminases are not significative for anyone of our outcomes and it is the first study to analyze also this subgroup of patients.

Regarding mortality, transaminases are not predictors but we found age, sex and CRP at day 1 as possible risk factors.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1: STROBE check-list

Supplementary Table 2: AST, ALT, CRP and LDH values at day 1 and at day 7 according to the presence of respiratory failure at admission

	Day 1			***Day 7***		
	Respiratory failure	*NO respiratory failure*	*p-value*	*Respiratory failure*	*NO respiratory failure*	p-value
CRP *median*	13 (4-17)	4 (2-10)	<0.001	12,5 (5-23)	16 (6-42,25)	0.002
AST *median*	53 (33,5-73,75)	31,5 (24-55,5)	<0.001	47 (29-67,5)	33 (22-55,5)	0.001
ALT *median*	39 (26-60,75)	30 (22-52)	0.03	45 (28-73,75)	37 (25-69,5)	0.09
LDH *median*	400 (300-512,75)	288 (234,5-387,5)	<0.001	384 (296,5-517,5)	266 (223-345,5)	<0.001

Supplementary Table 3: Prevalence of transaminases elevation at day 1 and at day 7, in patients with and without respiratory failure at admission

	Overall			*Respiratory failure*			*NO Respiratory failure*		
	Normal n (%)	< 2N n (%)	>2N n (%)	Normal n (%)	< 2N n (%)	>2N n (%)	Normal n (%)	< 2N n (%)	>2N n (%)
AST U/L day1	158/321 (49.2%)	113/321 (35,2%)	50/321 (15,6%)	43/131 (32.8%)	68/131 (51.9%)	20/131 (15.3%)	115/183 (62.8%)	41/183 (22.4%)	27/183 (14.8%)
ALT U/L day1	134/292 (45.9%)	105/292 (35.9%)	53/292 (18,2%)	63/135 (46.7%)	49/135 (36.3%)	23/135 (17%)	71/157 (45.2%)	56/157 (35.7%)	30/157 (19,1%)
AST U/L day7	151/290 (52.1%)	97/290 (33.4%)	42/290 (14,5%)	50/123 (40.6%)	51/123 (41.5%)	22/123 (17,9%)	101/167 (60.5%)	46/167 (27.5%)	20/167 (12 %)
ALT U/L day7	139/290 (47.9%)	84/290 (29.0%)	67/290 (23,1%)	50/123 (40.6%)	44/123 (35.8%)	29/123 (23,6%)	89/167 (53.3%)	40/167 (23.9%)	38/167 (22,8%)

Supplementary Table 4: Clinical features of patients with pre-existing liver disease

PATIENTS WITH CHRONIC LIVER DISEASE (n)	**12**
- ***Cirrhosis***	**4**
- ***Chronic Viral Hepatitis***	**3**
- ***NAFLD/NASH***	**5**
Age median	64 (56-74)
Female {n (%)}	2 (16.7)
Comorbidities	
Hypertension {n (%)}	9 (75.0)
Diabetes {n (%)}	5 (41,7)
Obesity {n (%)}	3 (25,0)
Cardiological comorbidities {n (%)}	2 (16.7)
Oncological comorbidities {n (%)}	1 (8.3)
Pneumological comorbidities {n (%)}	1 (8.3)
Nephrological comorbidities {n (%)}	2 (16.7)
Reumathological comorbidities {n (%)}	0 (0)
Onset Symptoms	
Respiratory Failure at admission {n (%)}	9 (75.0)
Fever {n (%)}	10 (83,3)
Gastrointestinal symptoms {n (%)}	1 (8.3)
Neurological symptoms {n (%)}	1 (8.3)
Ventilation at admission	
No ventilation	3 (25.0)
Nasal cannula/Venturi Mask	5 (41.7)
Reservoir Mask	4 (33.3)
CPAP	0 (0)
Laboratory findings	
AST at admission {median (IQR)} U/L	45 (27-63.5)
AST at day 7 {median (IQR)} U/L	40 (25-58)
ALT at admission {median (IQR)} U/L	33 (24-54)
ALT at day 7 {median (IQR)} U/L	41 (26-68)
CRP at admission {median (IQR)} mg/dl	7 (2.3-14)
PCR at day 7 {median (IQR)} mg/dl	12 (4-22.2)
LDH at admission {median (IQR)} U/L	327 (256-462)
LDH at day 7 {median (IQR)} U/L	302 (242-413)

