



COVID-19-Associated Liver Injury is a Key Determinant of Patient's Survival in a Low Endemicity Area from Central Italy

Ilaria L^{1*}, Andrea A¹, Vincenzo M², Marco I², Elisabetta T², Andrea Di L², Loredana S², Mario A¹ and Massimo A²

¹Hepatology Unit, Policlinico Tor Vergata, Department of Systems Medicine, Tor Vergata University, Rome, Italy

²Infectious Diseases Clinic, Policlinico Tor Vergata, Department of Systems Medicine, Tor Vergata University, Rome, Italy

Research Article

Volume 5 Issue 2

Received Date: August 26, 2020

Published Date: September 09, 2020

DOI: 10.23880/ghij-16000174

*Corresponding author: Ilaria Lenci, Hepatology Unit, Policlinico Tor Vergata, Tor Vergata University, Viale Oxford, Rome, Tel: +39 06 20900349; Email: ilaria.lenci@uniroma2.it

Abstract

Background: Liver injury (LI) occurring in patients with COVID-19 has been reported, yet its prognostic significance remains unexplored.

Aim: To investigate whether the onset, type and severity of virus-associated LI predicts the clinical outcomes of the disease

Methods: All consecutive patients with COVID-19 admitted to the Infectious Disease Unit of the University Hospital of Rome "Tor Vergata" from February to May 2020, were enrolled. LI was defined as the presence of an elevation of aminotransferases, gamma-glutamyl transferase or alkaline phosphatase greater than 1.5 times above the upper limit of normality (ULN), and/or a total bilirubin greater than 2.0 mg/dl. Death was considered as the primary endpoint.

Results: Among 151 hospitalized patients (mean age, 64 ± 18 years; 62.9% males) 41 (27.1%) died. LI was found in 57.6% of cases and in 23.8% was already present at admission. LI was associated with older age (p=0.006), longer hospital stay (p<0.0001), ICU admission (p=0.002), obesity (p=0.019) and cardiovascular diseases (p=0.029). Patients who died were older (p<0.0001), were more frequently admitted in ICU (p<0.0001) and had more comorbidities (40/41 patients; p<0.0001). Among 41 patients who died, 32 (78%) had LI (p=0.002) and the presence of this condition at admission was a significant predictor of lower survival (35 vs 49 days; p=0.030). At multivariate analysis, low albumin (p<0.0001), low ALT (p=0.0002), high AST (p=0.0250), high LDH (p=0.0014), low platelet count (p=0.0056) and high white blood cell count (p=0.0001) were independently associated with a greater risk of death.

Conclusion: LI occurs frequently in COVID-19 and its early emergence is an unfavourable prognostic marker of disease and clinical outcomes.

Keywords: SARS-Cov-2; COVID-19; Liver Injury; Survival

Abbreviations: ICU: Intensive Care Unit; AST: Aspartate Amino-Transferase; ALT: Alanine Amino-Transferase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; LI: Liver Injury; WBC: White Blood Cell; NEU: Neutrophils;

LYM: Lymphocytes; INR: International Normalised Ratio; LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein.

Introduction

SARS-CoV-2 was recently identified as a novel highly contagious and pathogenic coronavirus causing severe pneumonia. Since December 2019, the viral infection rapidly spread over the world, with more than 12 million of infected cases and over 560,000 related deaths reported to date [1]. The coronavirus disease 2019 (COVID-19) primarily involves the lungs, causing typical respiratory symptoms and signs. However, gastrointestinal symptoms and liver injury (LI) also occur during the course of the disease. Diarrhea has been reported as the most common digestive symptom, more often occurring within the first week of illness [2], and many COVID-19 patients presented abnormal liver enzymes, a feature possibly related to the disease severity [1]. The mechanisms of gastrointestinal and liver involvement by SARS-CoV-2 likely imply a primary role of angiotensin-converting enzyme 2 (ACE2) cell entry receptors, which are used by the virus to infect different epithelial cells. ACE2 receptors are in fact widely expressed in human small intestinal enterocytes [4], as in bile duct epithelial cells, but not in liver cells [5,6]. This suggests that ACE2 receptors are not directly involved in the development of SARS-CoV-2-induced hepatic damage, which rather may conceivably be the result of a systemic cytokine-mediated inflammatory response.

Since March 2019, several hospital-based studies have reported the clinical characteristics of patients with COVID-19, showing different patterns of liver abnormalities, with predominant hepatocellular, cholestatic or mixed damage [7-12]. Additionally, post-mortem pathological analyses performed in patients died from COVID-19 showed the presence of hepatocyte degeneration associated with lobular focal necrosis and neutrophil infiltration, as well as lymphocytes and monocytes infiltration in portal tracts and congestion of hepatic sinusoids, with evidence of microthrombosis [13,14]. Yet, histological features of liver failure or bile duct injury have not been observed in deceased cases. In a recent study from China [15], 41% of patients with COVID-19 showed abnormal liver tests at hospital admission and 5% had liver injury, based on liver enzyme abnormalities. Patients with abnormal liver tests were older, had a higher body mass index (BMI) and were more often males and had a greater risk of developing severe COVID-19 compared to those with normal liver function. A recent Italian meta-analysis [16], including 11 observational studies with more than 2000 patients with COVID-19, reported a relatively low prevalence (3%) of chronic liver disease at baseline in patients. However, patients with severe forms of COVID-19 developed more frequently abnormalities of liver enzymes and changes in the coagulative and fibrinolytic profiles. While the clinical characteristics of LI occurring in patients with COVID-19 have been extensively reported, little attention has

been given so far to the prognostic significance of COVID-19-associated LI, which therefore remains largely unexplored. It is also unclear whether LI presents with the same features in geographic areas with different rates of disease endemicity.

In this study of a cohort of SARS-CoV-2-infected patients consecutively admitted to a COVID hospital located in an area of central Italy with a cumulative incidence of 138,51 cases per 100,000 citizens [17], we aimed to investigate to what extent the onset, type and severity of virus-associated LI predicted the clinical outcomes of the disease.

Patients and Methods

This is a single-center, observational study evaluating the prevalence and the possible clinical impact of LI in patients with COVID-19 admitted to the Clinical Infectious Disease Unit of the Tor Vergata University Hospital in Rome, Italy. Patients' clinical features and laboratory tests were prospectively collected in a dedicated dataset. In particular, serology for hepatitis B and C viruses were evaluated in all patients at entry. All therapeutic regimens were reported and analysed. Liver injury was defined as the presence of aspartate amino-transferase (AST), alanine amino-transferase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase greater than 1.5 times the upper limit of normal values (ULN) (34 U/l, 55 U/l, 50 U/l and 150 U/l, respectively), or by the presence of total bilirubin greater than 2.0 mg/dl. LI was assessed both at hospital admission as well as if developed during the hospital stay and was classified as cytolytic, cholestatic or mixed type depending on the predominantly observed liver abnormality. Severe LI was defined by the presence of any serum liver test greater than 3 times above ULN.

The aim of the study was to assess whether LI predicts the clinical outcomes, considering death as the primary endpoint.

The study was conducted in compliance with the 1975 Declaration of Helsinki and was approved by our local Ethics Committee. (se disponibile mettere il numero dell'approvazione)

Statistical analysis

Chi-square with Mantel-Haenszel correction or Fisher-exact test were performed to compare categorical variables. A Kolmogorov-Smirnov test for normality was preliminarily executed to define the distribution of each continuous variable; a t-Student test was then performed for normally distributed variables and a Mann-Whitney U non-parametric test for non-normally distributed variables. A backward stepwise multivariable regression model was used to assess

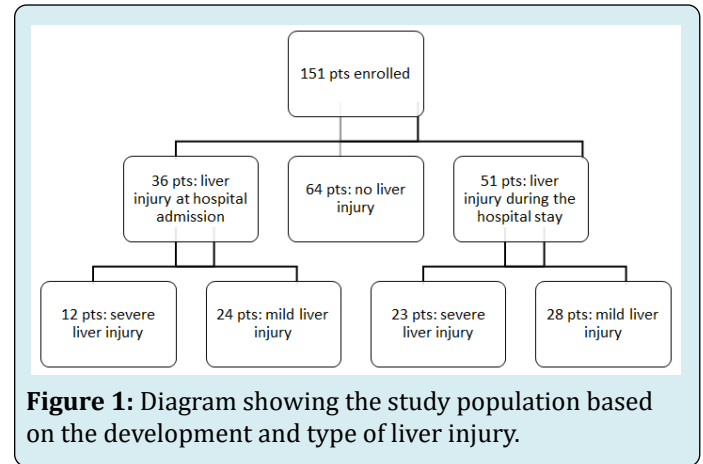
the association between all recorded patients' features and death. Survival was estimated using Kaplan-Meier curves and analysed by the log-rank test. A Cox regression analysis was performed to define the independent predictors of death recorded at time of hospitalization. Statistical significance was defined by a p value <0.05 in a "two-tailed" test, with a 95% confidence interval. Statistical analyses were performed using the IBM Statistical Program for Social Sciences (SPSS®) version 20.0 for Windows® (IBM Corp, Armonk, NY, USA).

Results

Prevalence and Severity of Liver Injury and Associated Factors

A total of 151 patients with COVID-19 were enrolled from February 27, 2020 to May 4, 2020 (Figure 1). As shown in Table 1, mean age was 64 ± 18 years with a prevalence of male gender (62.9%). The most frequent comorbidities were cardiovascular diseases (51.0%), pulmonary diseases

(24.5%) and diabetes (23.2%). Six patients were HCV-antibody positive and 2 of these had evidence of viral replication. No replicating HBV infections were observed. A total of 41 patients died during the observation period.



	Total (151 pts)	Liver Injury (87 pts)	No Liver Injury (64 pts)	P value	O.R.
Age (years)	64 ± 18	68 ± 16	60 ± 20	0.006	n.a.
Male Sex (%)	95 (62.9)	59 (67.8)	36 (56.3)	0.146	
Hospital stay (days)	20 ± 16	24 ± 17	14 ± 13	<0.0001	n.a.
ICU stay (%)	23 (15.2)	20 (23.0)	3 (4.7)	0.002	6.07
ICU stay (days)	8 ± 6	8 ± 6	12 ± 5	0.279	
Death (%)	41 (27.2)	32 (36.8)	9 (14.1)	0.002	3.556
Obesity (%)	27 (17.9)	21 (24.1)	6 (9.4)	0.019	3.076
Diabetes (%)	35 (23.2)	23 (26.4)	12 (18.8)	0.269	
Cardiovascular disease (%)	77 (51.0)	51 (58.6)	26 (40.6)	0.029	2.071
Liver disease (%)	2 (1.3)	1 (1.1)	1 (1.6)	0.826	
Pulmonary disease (%)	37 (24.5)	25 (28.7)	12 (18.8)	0.159	
Chronic Kidney disease (%)	14 (9.3)	8 (9.2)	6 (9.4)	0.97	
Cytopathic LI (%)	47 (31.1)	47 (54.0)	-		
Cholestatic LI (%)	8 (5.3)	8 (9.2)	-		
Mixed LI (%)	32 (21.2)	32 (36.8)	-		
Mild LI (%)	43 (28.5)	43 (49.4)	-		
Severe LI (%)	44 (29.1)	44 (50.6)	-		
LI at hospital admission (%)	36 (23.8)	36 (41.4)	-		
Cytopathic LI (%)	22 (14.6)	22 (25.3)	-		
Cholestatic LI (%)	4 (2.6)	4 (4.6)	-		
Mixed LI (%)	10 (6.6)	10 (11.5)	-		
Mild LI (%)	24 (15.9)	24 (27.6)	-		
Severe LI (%)	12 (7.9)	12 (13.8)	-		

HCV-ab positive (%)	6 (4.0)	4 (4.6)	2 (3.1)	0.672	
HCV-RNA positive (%)	2 (33.3)	1 (1.1)	1 (1.6)	0.807	
HBsAg (%)	0 (0.0)	0 (0.0)	0 (0.0)	-	
HBcAb (%)	25 (16.6)	19 (21.8)	6 (9.4)	0.064	
HBsAb (%)	34 (22.5)	21 (24.1)	13 (20.3)	0.71	
Lopinavir/Ritonavir (%)	112 (74.2)	67 (77.0)	45 (70.3)	0.353	
Hydroxychloroquine (%)	126 (83.4)	77 (88.5)	49 (76.6)	0.051	
Corticosteroids (%)	45 (29.8)	31 (35.6)	14 (21.9)	0.068	
Darunavir/Ritonavir (%)	28 (18.5)	18 (20.7)	10 (15.6)	0.429	
Tocilizumab (%)	27 (17.9)	20 (23.0)	7 (10.9)	0.056	

Table 1: Association between liver injury and patients' features.

All continuous variables are expressed as Mean \pm Standard Deviation.

Abbreviations: pts= patients; n.a. = not applicable; ICU= Intensive Care Unit; AST: aspartate amino-transferase; ALT: alanine amino-transferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; LI: liver injury.

LI was found in 87 patients (57.6%) and in 36 (23.8 %) of these was already present at hospital admission. LI was cytolytic in 47 patients (31.1 %), cholestatic in 8 patients (5.3%) and mixed type in 32 patients (21.2%), respectively. Severe LI was observed in 44 patients (29.1 %), in 12 of whom (27.2%) was already present at hospital admission. The mean hospital stay was significantly longer in patients with than without LI (24 \pm 17 vs 14 \pm 13 days, respectively, $p < 0.0001$). At univariate analysis, the following variables were found to be associated with LI: older age (68 \pm 16 vs 60 \pm 20 years; $p = 0.006$); ICU stay (23.0% vs 4.7%; $p = 0.002$); obesity (24.1% vs 9.4%; $p = 0.019$) and cardiovascular diseases (58.6% vs 40.6; $p = 0.029$).

A further sub-analysis was performed to define the characteristics of patients who developed severe LI. These patients presented more frequently with a mixed type of LI

($p = 0.034$) and more often were treated with tocilizumab and corticosteroids ($p = 0.006$ and $p = 0.023$, respectively), compared to those who did not show LI, or had only mild LI.

Liver Injury as Predictor of Death

Table 2 reports the characteristics of patients who died at univariate analysis. These patients were older (78 \pm 13 vs 59 \pm 17 years; $p < 0.0001$), more frequently admitted to ICU (39.0% vs 6.4%; $p < 0.0001$) and almost all had comorbidities (40/41 patients; $p < 0.0001$). LI was found in 32 patients who died (78.0%) compared to 55 (50.0%) who survived ($p = 0.002$). Patients who died showed higher levels of AST (67 \pm 75 vs 35 \pm 17 U/l; $p < 0.0001$), total bilirubin (0.91 \pm 0.49 vs 0.69 \pm 0.22 mg/dl; $p = 0.036$), GGT (61 \pm 71 vs 47 \pm 59 U/l; $p = 0.041$) and alkaline phosphatase (92 \pm 47 vs 66 \pm 27 U/l; $p < 0.0001$) than patients who survived.

	Death (41 pts)	Healed (110 pts)	P value	O.R.
Age	78 \pm 13	59 \pm 17	<0.0001	n.a
Male Sex (%)	25 (61.0)	70 (63.6)	0.763	
Hospital stay (days)	17 \pm 16	21 \pm 16	0.044	n.a
ICU stay (%)	16 (39.0)	7 (6.4)	<0.0001	9.147
ICU stay (days)	7 \pm 6	11 \pm 5	0.076	
Comorbidities (%)	40 (97.6)	63 (57.3)	<0.0001	29.841
Obesity (%)	9 (22.0)	18 (16.4)	0.426	
Diabetes (%)	18 (43.9)	17 (15.5)	<0.0001	4.281
Cardiovascular disease (%)	33 (80.5)	44 (40.0)	<0.0001	6.188
Liver disease (%)	0 (0.0)	2 (1.8)	0.945	
Pulmonary disease (%)	17 (41.5)	20 (18.2)	0.003	3.188

Chronic Kidney disease (%)	9 (22.0)	5 (4.5)	0.001	5.906
Liver injury (%)	32 (78.0)	55 (50.0)	0.002	3.556
AST	67 ± 75	35 ± 17	<0.0001	n.a
ALT	40 ± 43	52 ± 49	0.052	
Albumin	2.83 ± 0.36	3.65 ± 0.49	<0.0001	n.a
Total Bilirubin	0.91 ± 0.49	0.69 ± 0.22	0.036	n.a
GGT	61 ± 71	47 ± 59	0.041	n.a
ALP	92 ± 47	66 ± 27	<0.0001	n.a
Mild LI (%)	13 (31.7)	29 (26.4)	0.516	
Severe LI (%)	14 (34.1)	23 (20.9)	0.096	
LI at hospital admission (%)	15 (36.6)	21 (19.1)	0.025	2.445

Table 2: Factors associated with death at univariate analysis.

All continuous variables are expressed as Mean ± Standard Deviation.

Abbreviations: pts= patients; n.a. = not applicable; ICU= Intensive Care Unit; AST: aspartate amino-transferase; ALT: alanine amino-transferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; LI: liver injury.

In contrast, ALT values were lower in patients who died than in survivors, but the difference did not achieve statistical significance (40 ± 43 vs 52 ± 49 U/l; $p=0.052$). Albumin levels were lower in patients who died than patients who survived (2.86 ± 0.36 vs 3.65 ± 0.49 g/dl; $p<0.0001$). Even LI at admission was tightly related to a poor outcome, as it was observed in 36.6% of those who died compared to

19.1% of those who survived ($p=0.025$). Accordingly, the overall survival in patients with LI at hospital admission was significantly lower than in patients with normal liver function at entry (35 vs 49 days; $p=0.030$; Figure 2). Additional factors associated with death at univariate analysis are shown in supplementary Table 1.

	Death (41 pts)	Healed (110 pts)	P value
Corticosteroids (%)	23 (56.1)	22 (20.0)	<0.0001
Haemoglobin	11.4 ± 1.9	12.6 ± 1.8	0.001
WBC	11325 ± 4270	6630 ± 1880	<0.0001
NEU	9915 ± 4170	4485 ± 1845	<0.0001
LYM	825 ± 385	1440 ± 575	<0.0001
Platelets	212 ± 85	254 ± 80	0.003
INR	1.42 ± 0.69	1.15 ± 0.14	<0.0001
D-Dimer	6095 ± 8836	1616 ± 2456	<0.0001
Glycaemia	150 ± 53	110 ± 41	<0.0001
Creatinine	2.25 ± 1.79	1.03 ± 0.99	<0.0001
LDH	499 ± 234	260 ± 71	<0.0001
CRP	106.5 ± 51.5	39.9 ± 39.8	<0.0001

Supplementary Table 1: Additional factors associated with death at univariate analysis.

All continuous variables are expressed as Mean ± standard deviation.

Abbreviations: pts: patients; WBC: white blood cell; NEU: neutrophils; LYM: lymphocytes; INR: international normalised ratio; LDH: lactate dehydrogenase; CRP: C-reactive protein.

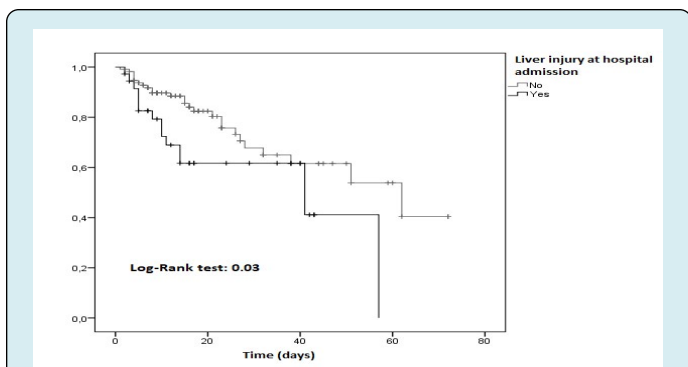


Figure 2: Kaplan-Meier estimated survivorship curve of patients with and without COVID-19-related liver injury.

All variables found to be significantly associated with death at univariate analysis were entered in a multivariable analysis model with COVID-19 death as dependent variable. The following variables, expressed as means during the whole hospital stay, were found to be independently associated with a greater risk of death: low albumin ($p<0.0001$), low ALT ($p=0.0002$), high AST ($p=0.0250$), high LDH ($p=0.0014$), low platelets count ($p=0.0056$) and high white blood cell count ($p=0.0001$).

We also performed a further analysis to identify which laboratory test measured at time of hospital admission was associated with a greater probability of death. These included, at univariate analysis, low haemoglobin ($p=0.001$), high white blood cells count ($p<0.0001$), high INR ($p=0.006$), high D-Dimer ($p=0.005$), high serum creatinine ($p<0.0001$),

high AST ($p=0.032$), high total bilirubin ($p=0.013$), high GGT ($p=0.041$), high alkaline phosphatase ($p<0.0001$), low serum albumin ($p<0.0001$), high LDH ($p<0.0001$) and high CRP ($p<0.0001$). All these variables were then entered in a Cox regression model, together with age, gender and the presence of individual comorbidities found to be associated with death in the previous analysis. Older age (H.R. 1.065, C.I. 95% 1.022-1.110; $p=0.003$), diabetes (H.R. 3.389, C.I. 95% 1.188-9.668; $p=0.023$), low serum albumin (H.R. 0.118, C.I. 95% 0.035-0.399; $p=0.001$), high AST (H.R. 1.007, C.I. 95% 1.000-1.013; $p=0.035$), high total bilirubin (H.R. 9.199, C.I. 95% 2.396-35.314; $p=0.001$), high GGT (H.R. 1.032, C.I. 95% 1.016-1.048; $p<0.0001$) and low alkaline phosphatase (H.R. 0.968, C.I. 95% 0.952-0.985; $p<0.0001$) were identified as independent predictive factors of death in SARS-CoV-2 infected patients (Tables 3 & 4).

	Standardized Coefficient	P value
Albumin	-0.2967	<0.0001
ALT	-0.2390	0.0002
AST	0.1907	0.0250
LDH	0.2757	0.0014
Platelets	-0.1495	0.0056
White Blood Cells Count	0.2833	0.0001

Table 3: Factors associated with death at multivariable analysis.

Abbreviations: ALT: Alanine amino-transferase; AST: Aspartate amino-transferase; LDH: lactate dehydrogenase.

	Death (41 pts)	Healed (110 pts)	P value
Corticosteroids (%)	23 (56.1)	22 (20.0)	<0.0001
Haemoglobin	11.4 ± 1.9	12.6 ± 1.8	0.001
WBC	11325 ± 4270	6630 ± 1880	<0.0001
NEU	9915 ± 4170	4485 ± 1845	<0.0001
LYM	825 ± 385	1440 ± 575	<0.0001
Platelets	212 ± 85	254 ± 80	0.003
INR	1.42 ± 0.69	1.15 ± 0.14	<0.0001
D-Dimer	6095 ± 8836	1616 ± 2456	<0.0001
Glycaemia	150 ± 53	110 ± 41	<0.0001
Creatinine	2.25 ± 1.79	1.03 ± 0.99	<0.0001
LDH	499 ± 234	260 ± 71	<0.0001
CRP	106.5 ± 51.5	39.9 ± 39.8	<0.0001

Table 4: Independent predictive factors of death at hospital admission.

All continuous variables are expressed as Mean ± Standard Deviation.

Abbreviations: WBC: white blood cell; NEU: neutrophils; LYM: lymphocytes; INR: international normalised ratio; AST: aspartate amino-transferase; ALT: alanine amino-transferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; CRP: C-reactive protein.

Discussion

Development of LI has been already described in earlier reports on COVID-19 patients. Our study provides further evidences that LI is a very frequent event in this setting, as it was found in 57% of SARS-CoV-2-infected patients in our cohort. Comparison of the prevalence rates of LI with the current literature is, however, difficult due to the variable definitions of LI adopted in different studies [15,18,19]. In the present study we aimed to address for the first time whether emergence of LI is related to the outcome of COVID-19, specifically looking at the time of onset of LI, its predominant type and its severity. We found, at multivariable analysis, that LI was an independent predictor of poor outcome, as patients who developed LI had a significantly lower survival compared to those who maintained normal liver tests during the hospital stay. Interestingly, 23.8% of the whole cohort of patients already presented with LI at hospital admission and this subgroup of patients had the highest probability of death compared to all other patients. Thus, LI is an early event during the course of the disease and its prompt detection upon entering the hospital, may help identifying patients with a poorer prognosis.

The origin of LI in patients with COVID-19 is currently unknown, yet it is most likely to be multifactorial. LI might in fact be the results of direct viral infection of liver epithelial cells, or follow a strong systemic inflammatory response, or be due to pneumonia-associated hypoxia. In addition, LI may be induced by sepsis-related metabolic acidosis and/or antiviral drug toxicity. Many of these putative mechanisms may indeed coexist and together conceivably trigger an ischemic/hypoxic pathway leading to liver damage, as the likely predominant cause. This interpretation is supported by our finding that an increase of AST and of LDH, observed either at or during hospitalization, but not an increase of ALT, was significantly associated with a greater risk of death, as already observed by Lei Fang et al. [20]. The possibility of a predominant ischemic/hypoxic nature of LI in COVID-19 is also consistent with the known ability of the virus to cause diffuse micro-thrombosis, associated with high D-Dimer values, as also found in our study in patients with worse outcomes. On the other hand, the possibility of a direct virus-related cytopathic damage appears less likely, also considering that none of the patients with LI died of acute liver failure or presented a clinically significant liver disease. Accordingly, liver biopsies were not performed to further investigate the nature of LI, as there was no clinical justification to perform invasive examinations. However, in our study LI appeared to present in most cases with a cytolytic or mixed biochemical pattern, and only rarely with a predominantly cholestatic type. This finding differs from what reported in a cohort of Asian patients, where a predominantly cholestatic type of LI was described [15], suggesting that SARS-CoV-2-related liver

pathogenicity might reflect different host-virus interactions, or even patient-related genetic variability.

Our study has limitations. Our cohort is relatively small, yet has the advantage to originate from a single academic center and to include a series of consecutive patients, with a negligible number of missing data. Our facility is a university hospital located in central Italy, where the incidence of COVID-19 has been considerably lower compared to other Italian regions, such as Lombardy or other areas from other countries in which COVID-19 incidence was significantly higher.

Conclusion

LI is as an inherent finding in COVID-19, despite its development is unlikely to be clinically relevant, nor associated with liver failure. Yet, its early emergence represents an unfavorable prognostic marker of the disease and prompt detection is therefore advisable to better identify patients at greater risk of death.

Conflicts of Interest: All Authors have no conflict of interest

Funding: No Authors received any financial support for the manuscript

References

1. European Centre for Disease Prevention and Control (ECDC) (2020) COVID-19 situation update worldwide.
2. Guan WJ, Zheng yi Ni, Yu Hu, Wen-hua L, Chun-quan O, et al. (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 382(18): 1708-1720.
3. Zhang C, Lei S, Fu-Sheng W (2020) Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 5(5): 428-430.
4. Zhanga H, Hong-Bao Li, Jian-Rui L, Xiao-Ming L, Wei L, et al. (2020) Specific ACE2 expression in small intestinal enterocytes may cause gastrointestinal symptoms and injury after 2019-CoV Infection. *International Journal of Infectious Diseases* 96 (2020): 19-24.
5. Chai X, Longfei H, Yan Z, Weiyu H, Zhou L, et al. (2020) Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *bio-Rxiv*.
6. Liu M, Ting W, Yun Z, Yutong Z, Yutong Z, et al. (2020) Potential Role of ACE2 in Coronavirus Disease 2019 (COVID-19) Prevention and Management. *J Transl Int Med* 8(1): 9-19.

7. Chen N, Min Z, Min Z, Xuan D, Jieming Q, et al. (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395: 507-513.
8. Huang C, Yeming W, Xingwang Li, Lili R, Jianping Z (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395(10223): 497-506.
9. Tian S, Nan H, ing L, Kun C, Xuqin K, et al. (2020) Characteristics of COVID-19 infection in Beijing. *J Infect* 80: 401-406.
10. Yang W, Qiqi C, Le Q, Xiaoyang W, Zenghui C, et al. (2020) Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 80: 388-393.
11. Zhang JJ, Xiang D, Yi-Yuan C, Ya-Dong Y, Yi-Bin Y, et al. (2020) Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 75(7): 1730-1741.
12. Wang D, Bo H, Chang H, Fangfang Z, Xing L, et al. (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 323: 1061-1069.
13. Xu Z, Lei S, Yijin W, Jiyuan Z, Lei H, et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 8(4): S2213-2600.
14. Liu Q (2020) General anatomy report of novel coronavirus pneumonia patients. *Journal of Forensic Medicine* 36: 21-23.
15. Cai Q, Deliang H, Hong Y, Jun C, Lei L, et al. (2020) COVID-19: Abnormal liver function tests. *J Hepatol* 8278(20).
16. Mantovani A, Giorgia B, Andrea D (2020) Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. *Liver Int* 40(6): 1316-1320.
17. Jothimani D, Radhika V, Mohammed FA, Ilankumaran K, Mohamed R, et al. (2020) Covid-19 and liver. *J Hepatol* S0168-8278(20): 30377-30379.
18. Fan Z, Liping C, Jun L, Xin C, Jingmao Y, et al. (2020) Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 18(7): 1561-1566.
19. Fang L, Ye-Mao L, Feng Z, Juan-Juan Q, Peng Z, et al. (2020) Longitudinal association between markers of liver injury and mortality in COVID-19 in China. *Hepatology* 72(2): 389-398.

