Clinical, biochemical and pulmonary CT imaging features for hepatobiliary involvement in COVID-19

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Abstract

Introduction **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a viral disease with primary pulmonary involvement and systemic impact. This article aims to assess the importance of clinical, biological, demographic and radioimaging parameters in COVID-19 patients in characterizing the incidence and severity of the hepatobiliary involvement.**

Methods **We performed an observational cohort study on 132 consecutive patients, evaluating their demographics, hospitalization period, peripheral oxygen saturation (SpO_2) in the ambient air, as well as biochemical markers of hepatobiliary involvement: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), direct bilirubin (DB), gamma-glutamyl transferase (GGT), serum albumin, total serum proteins, D-dimers; coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR); inflammatory markers: fibrinogen, serum ferritin, C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis alpha (TNF-α). Hepatobiliary involvement was further stratified by type of affection pattern: hepatocytolysis, cholestasis or mixed type. All patients received a computerized tomography (CT) chest scan in the first or second day of hospital admission.**

Results **We observed lower SaO_2 and longer hospitalization days in patients with hepatobiliary involvement, as well as longer coagulation times (PT and INR), lower serum albumin and higher serum ferritin ($p<0.05$). No significant correlations have been found between the degree or type of pattern of lung involvement as seen on CT scans performed and biochemical liver changes.**

Conclusions **Hepatobiliary involvement occurred in 72% of patients in the study group, associated with longer hospitalization period, prolonged coagulation parameters, lower serum albumin levels, raised serum ferritin and CRP levels. Cholestatic and mixed types of injury were associated with higher ferritin levels, while mixed type alone presented higher D-dimers levels compared with the cholestatic or hepatocytolysis groups. No significant correlation was found between lung involvement by CT evaluation and hepatobiliary involvement.**

Keywords **SARS-CoV-2, liver involvement, hepatic cytolysis, cholestasis, COVID-19.**

Introduction

SARS-CoV-2 has a broad tissue tropism not only for lungs but also heart, liver, kidney, muscle, vessel endothelium, manifestations found in both adults and children.[1,2]

Liver involvement in COVID-19, caused by SARS-CoV-2 infection, has garnered increasing attention in the medical community. Considering the role of the liver in the general homeostasis (metabolism, detoxification,

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coagulation, immune response to infections), a liver injury may be associated with systemic changes which require an adjustment in the management of COVID-19 patients.

Studies have shown that in COVID-19 the liver may be affected in a variety of ways. For example, one study found that liver enzymes levels had increased plasmatic values in a significant percentage of COVID-19 patients, indicating possible liver injury.[1] Another study demonstrated that SARS-CoV-2 can infect and replicate in hepatic cells, leading to inflammation and fibrosis.[3] In addition, COVID-19 has been associated with an increased risk of acute liver injury and exacerbation of prior liver conditions, such as viral hepatitis (B or C).[4]

The mechanisms by which COVID-19 impacts the liver are not yet fully understood, and more research is needed to determine the specific role of the liver in the development and progression of the disease. It is also important to identify potential treatments for COVID-19-related liver injury, as well as strategies for preventing and mitigating the liver involvement in COVID-19.

This study aims to assess the value of demographic, clinical, biochemical and imaging factors in patients with COVID-19 in determining the incidence and severity of hepatobiliary involvement.

Methods

We conducted an observational cohort study on 132 consecutive patients diagnosed with COVID-19 admitted to our department in the National Institute of Infectious Diseases "Prof. Dr. Matei Balş" between March 2021 and June 2021, divided into two groups: Group A (95 patients with biological markers of hepatobiliary involvement) and Group B (37 patients without biological markers of hepatobiliary involvement). Group A was further separated into three other cohorts as follows: A1 (26 patients with hepatocytolysis), A2 (12 patients with cholestasis), A3 (57 patients with both hepatocytolysis and cholestasis, mixed type). The population cohort sample parameters were a confidence level of 95%, a margin of error of 5%, and the population proportion at 5.4% (the prevalence of COVID-19 cases in our country from official reports at the time of the study[5]), resulting a minimum sample size of 79 patients.

We considered patients to have hepatobiliary involvement in case of elevated serum levels of ALT over 35 IU/L, AST over 36 IU/L, total bilirubin over 1.3 mg/dL, direct bilirubin over 0.4 mg/dL, GGT over 43 IU/L. Hepatocytolytic syndrome was defined as elevation of only ALT and AST, while cholestasis was defined solely by elevation of GGT and total bilirubin. Based on these definitions we divided the study group (Group A) into the three cohorts (A1, A2 and A3) mentioned above.

The data presented in this article are part of a more extensive research process regarding COVID-19, the methodology used in this article being also used in our previous published work.[6] The patients' data were collected on the day of admission.

The following inclusion criteria were applied: patients over 18 years old, positive COVID-19 test by real time-polymerase chain reaction (RT-PCR) method, and chest computerized tomography (CT) during their first two days of hospital admission.[6]

The exclusion criteria were defined as: patients younger than 18, pregnant and/or breastfeeding women, patients with known hepatic disease before admission (viral, autoimmune, toxic hepatopathy), and chronic kidney disease.[6] Patients on hepato-toxic medication were also excluded.

Demographic, clinical and biologic parameters

For each participant we registered the following parameters: age, sex, hospitalization period, peripheral oxygen saturation (SpO2) in the atmospheric air, systolic and diastolic blood pressure, heart rate, respiratory rate, biochemical markers of hepatobiliary dysfunction (ALT, AST, total and direct bilirubin, GGT), inflammatory markers (C reactive protein (CRP), fibrinogen, serum ferritin, interleukin-6 (IL-6), tumor

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necrosis factor alpha (TNFα)), D-dimers, serum albumin and total serum proteins, coagulation markers (PT, INR and aPTT), as well as radio-imaging parameters by CT-scans, as described below.[6]

Radio-imaging parameters

Severity of lung disease was graded from 0 to 3 considering the number of pulmonary segments with pneumonia. We quantified the number of pulmonary segments with interstitial pneumonia and alveolar consolidation (0 to 19), the number of pulmonary lobes with pneumonia (1 to 5), the type of lung involvement (unilateral or bilateral), the presence of crazy paving pattern (grade 1 to 3), vascular ectasia (grade 0 to 2), fibro-atelectatic changes (grade 0 to 3), the presence of mediastinal adenopathies, pericardial effusion and pleural effusion.[6]

Two radiologists (ED and ML) with 5 and 20 years of experience evaluated the CT examinations, while blinded towards the identity, demographic, clinical, and biological parameters of the patients.

Statistical evaluation

We used for statistical analysis the Statistical Package for Social Sciences (SPSS version 25, IBM Corp., USA); patient data are presented as medians and quartiles (Q1, Q3) for continuous variables and as percentages for the categorical variables.[6]

Significant correlations between independent variables and liver involvement were established with Spearman's equation.

We evaluated the impact of all parameters on abnormal liver biomarkers using binary logistic regression univariate analyses with the registered data as the independent variables and modified hepatic markers as the dependent variable.[6]

Furthermore, analysis of variance (ANOVA) tests were performed to evaluate which parameters were significantly correlated with liver involvement in our subgroups (hepatocytolysis, cholestasis and mixed type), with LSD post-hoc analysis to further characterize individual relationships between the type of liver involvement and demographic, clinical, biochemical or imaging parameters.

Variables with significant association with liver involvement ($p<0.05$) were grouped into clinical, biological, and demographic, as well as lung imaging parameters.[6]

The principles of the Declaration of Helsinki were met and the study was approved by the local institute ethical committee (C10218/15.09.2021).

Results

Group A consisted of patients with biochemical markers of liver involvement and included 95 patients (72%) - 56 males (59%) and 39 females (41%). These patients were further separated in three groups by type of involvement. Thus, group A1 consisted of 26 patients with hepatocytolysis, signified by only elevation of ALT or AST - 11 males and 15 females, group A2 consisted of 12 patients with cholestasis, characterized by only elevation of total bilirubin or GGT - 5 males and 7 females, group A3 consisted of 57 patients with mixed type, signified by hepatocytolysis and cholestasis - 40 males and 17 females. Group B consisted of patients without biochemical markers of liver involvement and included 37 patients (28%) - 13 males (36%) and 24 females (64%).

All admitted patients presented a positive COVID-19 rt-PCR test. The median timeframe from the positive rt-PCR test was 2 days for both groups of patients, with interquartile ranges (IQR), Q1 and Q3 of 1(1.75; 3) for the patients in Group A and 2 (1; 3) for the patients in Group B.

Lower oxygen saturation rate (92% vs 97%) and longer hospitalization period (12 days vs 7 days) were seen in patients in group A versus group B ($p<0.05$). Similarly, significant lower serum albumin levels were observed in patients with liver involvement (3.8 g/dL vs. 4.1 g/dL, $p=0.011$), but still in the normal ranges. No correlations were found for total serum proteins levels. Serum ferritin was markedly elevated in patients in group A, but not in group B. Although coagulation markers were found to have significant differences as seen in Table 1, both INR and PT were in normal range for both groups.

We observed no statistically significant differences in the two study groups for C-reactive protein and D-dimers levels, even though they were also registered as higher in patients in group A (13.9 [4.4; 45.3] vs. 5.7 [1.2; 12.2]; 194 [117; 382] vs. 133 [82; 179]).

Following the imaging protocol and scoring described in chapter 2.2, no statistical difference was found in pattern or severity of lung affection between patients with and without hepatobiliary involvement (Table 2).

Hospitalization length, SaO_2 and serum ferritin levels showed the highest correlation with hepatobiliary involvement (Spearman's rho coefficient = 0.41; -0.36; 0.35) with statistical significance ($p<0.01$). As shown in Table 3, males, older age, elevated D-dimers and CRP, as well as lower serum albumin levels registered positive correlations with hepatobiliary involvement.

ANOVA analysis of the hepatobiliary involvement subgroups revealed statistically significant differences between the type of hepatobiliary involvement (cytolysis, cholestasis, mixed type) as shown in Table 4. Serum ferritin and CRP levels was significantly more elevated in the cholestasis and mixed type (subgroup A2 and A3), but not in the hepatocytolysis group (subgroup A1). Atelectatic changes were more prevalent in subgroup A3.

Discussion

In our research we found that a high percent (72%) of patients with COVID-19 presented hepatobiliary involvement, that is in accordance with other authors' results.[7]

Angiotensin-converting enzyme 2 (ACE2) receptors are known to be the main entry-point of the virions. Although discussion has been mainly concentrated on the high expression in type II alveolar cells, cholangiocytes also present a similar level of expression of ACE2 receptors, while Kupffer cells, hepatocytes and endothelial cells present a lower expression.[8] Levels of ACE2 receptors may be further raised by prior liver disease,[9] but these patients have been excluded from our cohort study. Direct infection and viral cytotoxicity are, thus, key hypothesized mechanisms of injury in liver tissue.

Searching the cell-specific expression of the ACE2 receptor in healthy liver cells, researchers found ACE2 to be expressed in 2.6% of hepatocytes and 59.7% of cholangiocytes, strongly indicating that hepatocytes injury may be caused by direct viral invasion.[10]

A recent study by Wu et al. suggests the probable viral replication in extrapulmonary sites (such as the digestive tract and liver). In patients with COVID-19, virus shedding in their fecal specimens was detected, up to 11 days after viral detection in respiratory tract became negative.[11]

Liver hypoxia due to gas exchange deficiencies secondary to lung injury, or to the presence of microthrombi in liver circulation, the drug induced toxicity and immune mediated are a few of the other proposed mechanisms of action in hepatobiliary involvement in patients with COVID-19.[8,9,12,13]

Several drugs that have been prescribed for COVID-19, such as lopinavir/ritonavir, ribavirin, tocilizumab, oseltamivir, can lead to hepatotoxicity in susceptible patients; however early administration of tocilizumab could be also contributing to the improved outcomes and significant radiological improvement.[14] Even if not all mechanisms are well-understood, a few drug pharmacological characteristics have been considered to cause liver injury: lipophilicity, liability in the mitochondria, the ability to generate reactive metabolites and to inhibit hepatic transporters.[15]

Additionally, lower oxygen saturations (SaO_2) in ambient air and longer hospitalization period may be in direct correlation with general degree of disease burden and not by liver mechanism alone, ACE2 receptors having close expression in type II alveolar cells and cholangiocytes, as mentioned earlier.

Guan et al. found that up to 4% of patients with COVID-19 had reduced albumin levels,[16] in contrast to our figure of 9%, possibly owing to our reduced cohort (n=132). Studies have shown an association with poorer prognosis between serum albumin levels and severe forms of pneumonia, longer hospitalization period and even mortality.[17,18] However, serum albumin should not be referred to as strictly a marker of reduced liver function, because of the possible

Table 1. Clinical and laboratory characteristics in patients with COVID-19 with and without hepatobiliary involvement

Evaluated parameter	Group A (patients with hepatobiliary involvement)	Group B (patients without hepatobiliary involvement)	p-value
SaO_2 (%)	92 [88.5; 96]	97 [94; 98]	**<0.001**
Hospitalization (days)	12 [9; 15]	7 [1; 11]	**<0.001**
Hemoglobin (g/dL)	14.1 [13.3; 15.2]	13.9 [12.7; 14.5]	0.612
RBC ($\times 10^6$/µL)	5.1 [4.3; 6.1]	5.4 [4.4; 5.9]	0.522
ALT (IU/L)	57 [36; 94]	22 [15.7; 28]	N/A
AST (IU/L)	44 [33; 65]	24.5 [20.7; 29]	N/A
TB (mg/dL)	0.7 [0.5; 0.9]	0.6 [0.5; 0.7]	N/A
DB (mg/dL)	0.2 [0.2; 0.3]	0.2 [0.1; 0.2]	N/A
GGT (IU/L)	70 [43.5; 119.7]	22.5 [16; 34.2]	N/A
Serum albumin (g/dL)	3.8 [3.5; 4.2]	4.2 [3.6; 4.7]	**0.011**
Total serum proteins (g/dL)	7.1 [6.6; 7.6]	7.2 [6.9; 7.7]	0.204
PT (sec)	12.6 [11.8; 13.9]	12 [11.5; 12.3]	**0.009**
aPTT (sec)	30.5 [27.8; 33.9]	29 [28; 30.6]	0.312
INR	1 [0.9; 1.1]	1 [0.9; 1]	**0.009**
D-Dimers HS (ng/mL)	194 [117; 382]	133 [82; 179]	0.426
CRP (mg/dL)	13.9 [4.4; 45.3]	5.7 [1.2; 12.2]	0.061
Fibrinogen (mg/dL)	404 [320.7; 522.2]	366.3 [282; 457.5]	0.101
Serum ferritin (ng/mL)	429.3 [208.6; 831.9]	106.7 [57.9; 278.5]	**0.006**
IL-6 (pg/mL)	12.5 [1.8; 105.1]	9.2 [3.9; 40.7]	0.815
TNF-α (pg/mL)	1.9 [0.3; 8.5]	0.9 [0; 10.7]	0.711

SaO2 – peripheral oxygen saturation in ambient air; **RBC** – red blood cells; **ALT** – alanine aminotransferase; **AST** – aspartate aminotransferase; **TB** – total bilirubin; **DB** – direct bilirubin; **GGT** – gamma-glutamyl transferase; **PT** – prothrombin time; **aPTT** – activated partial thromboplastin time; **INR** – international normalized ratio; **CRP** – C-reactive protein; **IL-6** – interleukin-6; **TNF-α** – tumor necrosis alpha; **N/A** – not applicable.
Patient data are presented as medians and quartiles [Q1–first quartile, Q3–third quartile].

Table 2. Radiological characteristics in patients with COVID-19 with and without hepatobiliary involvement

Imaging characteristics	Group A (patients with hepatobiliary involvement)	Group B (patients without hepatobiliary involvement)	p-value
Degree of lung injury	2 [1; 2]	1 [1; 2]	0.421
Number of pulmonary lobes with inflammatory changes	5 [3; 5]	5 [4; 5]	0.509
Degree of GGO involvement	1 [1; 2]	1 [1; 2]	0.825
Crazy paving aspect	1 [0; 2]	1 [0; 1]	0.110
Vascular ectasia	0 [0; 1]	0 [0; 1]	0.636
Bronchiectasis	0 [0; 1]	0 [0; 1]	0.312
Atelectatic changes	1 [0; 2]	1 [0; 1]	0.202
Consolidation areas	0 [0; 2]	0 [0; 1]	0.331
Mediastinal adenopathies	0 [0; 1]	0 [0; 1]	0.514

GGO – ground glass opacity.
Patient data are presented as medians and quartiles [Q1=first quartile, Q3=third quartile].

Table 3. Correlations of hepatobiliary involvement with demographic, clinical, biochemical and CT imaging parameters

Evaluated parameter	Spearman's rho coefficient	p-value
Sex (1= male; 2=female)	-0.21	**0.011**
Age	0.17	**0.042**
SaO_2 (%)	-0.36	**<0.001**
Hospitalization (days)	0.41	**<0.001**
Hemoglobin (g/dL)	-0.1	0.251
RBC ($\times 10^6/\mu L$)	-0.13	0.210
Serum albumin (g/dL)	-0.25	**0.031**
Total serum proteins (g/dL)	-0.12	0.330
PT (sec)	0.18	**0.032**
aPTT (sec)	1.12	0.231
INR	0.2	**0.024**
D-Dimers HS (ng/mL)	0.23	**0.012**
CRP (mg/dL)	0.23	**0.013**
Fibrinogen (mg/dL)	0.15	0.092
Serum ferritin (ng/mL)	0.35	**0.002**
IL-6 (pg/mL)	0.01	0.921
TNF-α (pg/mL)	0.1	0.453
Degree of lung injury	0.07	0.392
Number of pulmonary lobes with inflammatory changes	0.01	0.962
Degree of GGO involvement	-0.02	0.810
Crazy paving aspect	0.1	0.244
Vascular ectasia	0.01	0.853
Bronchiectasis	0.06	0.441
Atelectatic changes	0.1	0.261
Consolidation areas	0.08	0.332
Mediastinal adenopathies	0.05	0.530

RBC – red blood cells; **PT** – prothrombin time; **aPTT** – activated partial thromboplastin time; **CRP** – C-reactive protein; **IL-6** – interleukin-6; **TNF-α** – tumor necrosis alpha; **GGO** – ground glass opacity.

Table 4. Analysis of variance among subgroups of hepatobiliary involvement cohort and posthoc analysis

Evaluated parameter	Group A (patients with hepatobiliary involvement)				
	Group A1 (26 patients with hepatocytolysis)	Group A2 (12 patients with cholestasis)	Group A3 (57 patients with mixed involvement)	ANOVA p-value	LSD posthoc analysis (A1 vs A2, A2 vs A3, A1 vs A3)
SaO_2 (%)	92 [88; 96.2]	95 [93; 98]	90.5 [88.2;95]	0.432	0.532; 0.211; 0.407
Hospitalization (days)	13 [9; 15.7]	13.5 [8.5; 19.5]	12 [9; 15]	0.821	0.724; 0.935; 0.521
Hemoglobin (g/dL)	14.6 [13.9; 15.7]	15.1 [14.1; 15.5]	14.1 [13.1; 15.1]	0.331	0.312; 0.102; 0.422
RBC ($\times 10^6/\mu L$)	5.2 [4.4; 6.3]	5.3 [5.1; 6.2]	4.9 [4.1; 5.8]	0.416	0.611; 0.207; 0.333
ALT (IU/L)	49 [30.7; 64.2]	23 [17; 27]	80 [48; 121.5]	N/A	N/A
AST (IU/L)	40.5 [34.7; 51.7]	24 [20.2; 29.7]	53 [39; 76.5]	N/A	N/A
TB (mg/dL)	0.7 [0.5; 0.9]	0.7 [0.6; 0.9]	0.7 [0.5; 0.9]	N/A	N/A
DB (mg/dL)	0.2 [0.1; 0.3]	0.3 [0.3; 0.4]	0.2 [0.2; 0.3]	N/A	N/A
GGT (IU/L)	35 [27; 37]	81.5 [52.5; 116.7]	97 [62; 137]	N/A	N/A
Serum albumin (g/dL)	3.6 [3.4; 4.2]	4 [3.8; 4.2]	3.7 [3.5; 4.2]	0.522	0.314; 0.225; 0.934
Total serum proteins (g/dL)	6.9 [6.6; 7.6]	7.4 [6.8; 7.7]	7.1 [6.5; 7.6]	0.713	0.623; 0.415; 0.630
PT (sec)	13.3 [11.7; 14.4]	12.2 [11.3; 13.5]	12.6 [11.8; 13.9]	0.824	0.811; 0.621; 0.725
aPTT (sec)	31.1 [29.3; 36]	27.8 [27.3; 33.9]	30.1 [27.1; 32.5]	0.341	0.101; 0.327; 0.505
INR	1.1 [1; 1.1]	1 [0.9; 1.1]	1 [1; 1.1]	0.833	0,810; 0.614; 0.737
D-Dimers HS (ng/mL)	251 [95; 272]	117 [85; 404]	245 [143.5; 482]	**0.041**	0.604; 0.239; **0.010**
CRP (mg/dL)	7.8 [2.8; 31.5]	27.7 [19.1; 89.3]	13.2 [4.4; 52.9]	0.122	**0.031**; 0.107; 0.235
Fibrinogen (mg/dL)	380 [320.7; 520]	465 [326; 599.8]	404 [313; 524.5]	0.311	0.111; 0.223; 0.630
Serum ferritin (ng/mL)	216.4 [89.5; 597.4]	287.4 [116; 531.8]	627.3 [387.1; 1005.9]	**0.007**	0.734; **0.021; 0.007**
IL-6 (pg/mL)	7.3 [0.2; 29.4]	2.8 [1.4; 93.2]	19.3 [5.2; 156.3]	0.203	0.922; 0.218; 0.103
TNF-α (pg/mL)	1.5 [0.1; 13]	0.3 [0; 0.6]	4 [1.5; 9.7]	0.424	0.201; 0.711; 0.233
Degree of lung injury	1 [1; 2.2]	2 [1; 2.7]	2 [1; 2]	0.436	0.414; 0.805; 0.208
Number of pulmonary lobes with inflammatory changes	5 [2; 5]	5 [1; 5]	5 [4; 5]	0.425	0.913; 0.325; 0.419
Degree of GGO involvement	1 [0.7; 2]	1.5 [0.2; 2]	1 [1; 2]	0.914	0.808; 0.813; 0.936
Crazy paving aspect	1 [0; 1.2]	1 [0; 2]	1 [0. 1.5]	0.505	0.227; 0.512; 0.407
Vascular ectasia	0 [0; 1.2]	0 [0; 1]	0 [0; 1]	0.814	0.836; 0.617; 0.623
Bronchiectasis	0 [0; 1]	0 [0; 1]	0 [0; 1]	0.809	0.507; 0.522; 0.919
Atelectatic changes	0 [0; 1]	0.5 [0; 2]	1 [0; 2]	**0.012**	0.111; 0.708; **0.004**
Consolidation areas	0 [0; 2]	0 [0; 1.7]	0 [0; 1.5]	0.919	0.943; 0.926; 0.841
Mediastinal adenopathies	0 [0; 1]	0 [0; 1]	0 [0; 1]	0.727	0.417; 0.625; 0.628

SaO2 – peripheral oxygen saturation in ambient air; **RBC** – red blood cells; **ALT** – alanine aminotransferase; **AST** – aspartate aminotransferase; **TB** – total bilirubin; **DB** – direct bilirubin; **GGT** – gamma-glutamyl transferase; **PT** – prothrombin time; **aPTT** – activated partial thromboplastin time; **INR** – international normalized ratio; **CRP** – C-reactive protein; **IL-6** – interleukin-6; **TNF-α** – tumor necrosis alpha; **GGO** – ground glass opacity; **N/A** – not applicable. Patient data are presented as medians and quartiles [Q1=first quartile, Q3=third quartile].

mechanisms: prioritizing other protein synthesis (pro-inflammatory markers despite albumin synthesis as it is a negative acute phase protein), loss of proteins through gastrointestinal tract in patients with enteric manifestations in COVID-19, loss through the nephron glomerulus in kidney involvement, and even increased catabolism.

Serum ferritin, an acute phase reactant, indicates an activated monocyte-macrophage system, knowing that its synthesis is responsive to alteration in the cytokine status at a transcriptional and translational level.[19] Cheng L. and colleagues[20] have put together a meta-analysis that evaluated serum ferritin levels in patients with COVID-19, where it is shown the association with poor prognosis and valued as an

important predictor of worsening of COVID-19 patients. In a similar manner, Kaushal et al.[21] have found higher ferritin levels in COVID-19, with higher levels in patients with severe disease, requiring intensive care unit admission, even artificial ventilation, as well as in non-survivors.

We found that two types of hepatobiliary involvement are more prevalent (cholestasis or mixed types) and were associated with higher ferritin levels, while mixed type alone presented higher D-dimers levels compared with the cholestatic or hepatocytolysis groups. Thus, we revealed strong associations of serum ferritin levels with hepatobiliary involvement especially in cholestatic and mixed type, indicating the importance of serum ferritin as a biomarker of severity in COVID-19, in possible relation to cholangiocyte involvement.

We found a significant association between hepatobiliary involvement with increased CRP levels which indicates that both systemic inflammation and organ (liver) inflammation may play an important role in the development of hepatobiliary injury in patients with COVID-19, in accordance with the reported data.[22] The elevation of CRP levels has also been found significantly correlated with other organ injuries in COVID-19, such as heart and pericardial involvement.[23]

Both hepatobiliary and heart and pericardial involvements (myopericarditis) may be associated with increasing CRP levels as a result of persistent inflammation and organ damage; in addition, AST and ALT may also be found with increasing levels in these two types of organ damage in COVID-19, as they are not specific liver enzymes, and may have extrahepatic origin,[24] but also in other possible lung superinfections.[25] Routine chest CT imaging of patients on admission revealed only a minor association between hepatobiliary involvement and atelectasis in the mixed type subgroup, opposite of the hepatocytolysis and cholestasis subgroups.

One of the relevant strengths of the study is represented by the fact that it is one of the few studies that evaluates the liver involvement in patients with COVID-19 excluding other hepatic conditions and also any hepato-toxic medication. Another strength of our study is the presentation in a stratified manner of different types of liver involvement and the variance of the demographic, clinical, coagulation, biochemical and radio-imaging parameters in each specific subgroup.

Limitations of the study: the study is retrospective, has a relatively small number of patients and provides data recorded in a single study center. Liver biopsy was not performed and the characterization of liver involvement was based on biochemical data only.

Conclusions

In conclusion, hepatobiliary involvement represents an important complication in patients with COVID-19, with possible influence of disease prognosis and hospitalization period. Hepatobiliary involvement occurred in 72% of patients with COVID-19 and it was associated with male gender, older age, a longer hospitalization period, lower SaO_2, lower serum albumin levels, raised serum ferritin and CRP levels and prolonged coagulation parameters (PT and INR). Cholestatic and mixed types of injury were associated with higher ferritin levels, while mixed type alone presented higher D-dimers levels compared with the cholestatic or hepatocytolysis groups. No significant correlation was found between lung involvement by CT evaluation and hepatobiliary involvement.

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