Original Research

SARS-CoV-2 associated liver injury: a six-month follow-up analysis of liver function recovery

Adina Roman[1,2,3], Septimiu Moldovan[2,4], Mircea Stoian[2,4], Brîndușa Țilea[2,5], Daniela Dobru[1,2]

1) Gastroenterology Department, Mureș County Clinical Hospital, Târgu Mureș, Romania

2) "George Emil Palade" University of Medicine, Pharmacy, Sciences and Technology, Târgu Mureș, Romania

3) Doctoral School, "George Emil Palade" University of Medicine, Pharmacy, Sciences and Technology, Târgu Mureș, Romania

4) Intensive Care Unit, Mures County Clinical Hospital, Târgu Mureș, Romania

5) Infectious Diseases Department, Mures County Clinical Hospital, Târgu Mureș, Romania

Abstract

Background and aims. SARS-CoV-2 infection has raised the interest in clinical and paraclinical research worldwide, representing a public health issue since the beginning of 2020. Studies have established the variable, unpredictable character of COVID-19. Our main objective was to assess the liver function of patients without pre-existing liver disease, diagnosed with SARS-CoV-2 associated liver injury in a 6-month follow-up study after discharge from hospital.

Methods. We conducted a prospective paraclinical and imagingstic follow-up study between 1st September 2020 and 30th April 2021 on patients without pre-existing liver disease previously diagnosed with SARS-CoV-2 associated liver injury who had been admitted in Mures County Clinical Hospital, Targu Mures, Romania. We followed up the patients 'clinical and paraclinical datacharacteristics at index COVID-19 hospitalization and at T1 (6-month follow-up visit).

Results. We performed abdominal ultrasonography and laboratory examinations in 78 patients (mean age 45±10 years) hospitalized 6 months earlier for symptomatic COVID-19, with a male:female ratio of 1.3:1.
Thirty patients (38.46%) were discharged at index COVID-19 hospitalization with abnormal liver function tests, while the rest presented paraclinical normalization at discharge and mean duration of liver injury of approximately 7 days. Follow-up examination revealed abnormal liver function tests in twenty-four patients, most of which presented with mild liver injury. All patients with severe COVID-19 at index hospitalization presented with abnormal liver function tests at follow-up examination.

Conclusions. By performing a complete clinical and paraclinical 6-month follow-up study, with a specific focus on 34.6% of patients in which we noted a persistence of liver function tests abnormality, we could analyzse a possible long-term effect of SARS-CoV-2 infection over liver function and also raise awareness of liver function tests monitoring and therapeutic management in post COVID-19 patients. Long-term follow-up studies of COVID-19 multi-organ sequelae are therefore mandatory in order to improve the practice of consultant gastroenterologists.

Keywords: COVID-19, liver injury, SARS-COV2, liver function tests, follow-up study

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Address for correspondence:
adina.roman91@gmail.com

Background and aims

SARS-CoV-2 infection represented a global public health issue which has caught the interest of physicians and researchers since the beginning of 2020. The variable, unpredictable character of COVID-19 was established.

COVID-19 has affected up until present day over 220 countries and territories, with more than 180 million cases, and almost 4 million deaths [1]. On a comparative note, the impact of SARS-CoV infection in 2003 was associated with approximately 1000 deaths, and the swine flu pandemic in 2009-2010 caused approximately 600.000 deaths [2].

Large cohort-based studies performed on a large number of patients demonstrated the correlation between liver injury and SARS-CoV-2 infection. Statistical examinations proved the association between pulmonary specific lesions and abnormal liver function tests, as well as the relationship between steatohepatitis and viral aggression [3,4].

Up until now, the pathogenesis of SARS-CoV-2 associated liver injury has not been fully explained, due to diverse pathogenetic mechanisms involved. These include the interactions between SARS-CoV-2 spike and cellular receptors in the host organism, and furthermore the cellular membrane of hepatocytes [5], as well as ECA2 receptor expression at the level of cholangiocytes, being an additional risk factor to direct hepatocyte viral injury [6]. The choice of potentially hepatotoxic drugs such as Remdesivir, lopinavir/ritonavir, hydroxychloroquine or oseltamivir used in the current therapeutic scheme of COVID-19 cannot be excluded as a supplementary risk factor in SARS-CoV-2-associated liver injury [7]. Although their potentially hepatotoxic effect has been thoroughly researched, the European Association of the Study of Liver has recommended until present a close follow-up of this potential effect only in patients previously diagnosed with chronic liver disease and in patients who underwent an organ transplant, due to their associated immunosuppression, as the benefit of administering antiviral drugs was considered significantly higher [8].

Associated early complications with SARS-CoV-2 liver injury include acute liver injury, vascular thrombosis including the portal system, which led to a poor outcome of COVID-19 patients [9].

Our main objective was to assess the liver function of patients without pre-existing liver disease, diagnosed with SARS-CoV-2 associated liver injury. The current study aimed to establish the impact of persistent abnormal liver function tests on the recovery of COVID-19 patients.

The null hypothesis is that the persistence of the abnormality of liver function tests had no effect on the recovery or the poor outcome of SARS-CoV-2 patients.

Methods

We conducted a prospective paraclinical and imaging follow-up study between 1st September 2020 and 30th April 2021 on patients without pre-existing liver disease previously diagnosed with SARS-CoV-2 associated liver injury who had been admitted in Mures County Clinical Hospital, Targu Mures, Romania.

We followed up the patients' clinical and paraclinical characteristics at index COVID-19 hospitalization and at T1 (6-month follow-up visit).

Inclusion criteria

Adult patients, who were previously diagnosed with SARS-CoV-2-associated liver injury (abnormal liver function tests and laboratory detection of SARS-CoV-2 RNA), followed-up at a 6-month presentation after discharge.

Liver injury was further classified according to clinical studies [10] as mild (higher than three times of upper limit of normal values (ULN), less than five times ULN), moderate (5-10 times higher of ULN) and severe (higher than 10 times of ULN) and was defined as the presence of abnormal liver function tests (alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), gamma-glutamyl-transferase (GGT), alkaline phosphatase (AP) and total bilirubin (TB)).

Exclusion criteria

Adult patients with a history of pre-existing liver disease before the moment of SARS-CoV-2 detection or which were diagnosed during hospitalization with an additional common source of liver injury. Exclusion criteria of pre-existing liver disease included: patient case files, presence of reactive viral markers involved in chronic liver disease, autoimmune disease panel tests, investigation of dysmetabolic disorders as well as previous imaging findings, as presented in table I.

Table I. Algorithm of differential diagnosis performed in enrolled COVID-19 patients for the etiological diagnosis of liver injury. Adapted version [24].

Possible etiology	Examples of excluded pathology
Viral	Hepatitis A, E, B, C, Cytomegalovirus, Herpes Simplex Virus, Varicelo-Zoosterian Virus
Drugs/toxins	Paracetamol (acetaminophen), NSAID use, anti-tuberculous, chemotherapy, statins, phenytoin, carbamazepine
Vascular	Budd Chiari Hypoxic hepatitis
Other	Wilson disease Autoimmune hepatitis Primary sclerozing cholangitis Lymphoma Malignancy

Data collected included: demographics, associated comorbidities, data regarding clinical outcomes, laboratory tests during their admission and at follow-up visit including complete blood count, liver function tests, renal function, electrolyte count, biochemical tests and inflammatory markers, as well as imagistic examination (abdominal ultrasound, computed tomography scan) and complete etiological investigations.

For supplementary analysis, patients were included into two groups. Group 1 included patients which during admission (index hospitalization) presented with a non-severe form of COVID-19 and Group 2 patients with severe COVID-19 during admission.

The severity of COVID-19 was classified according to international guidelines, using criteria such as symptoms, clinical signs (the presence of hypoxemia) and paraclinical findings (inflammatory syndrome, chest X-Ray, thoracic CT scan results). Therefore, patients with mild illness were considered symptomatic patients without dyspnea or abnormal chest imaging. Moderate illness included patients with evidence of lower respiratory disease, but with an SpO2 (oxygen saturation) above 94% on room air. Severe illness included patients with SpO2 lower than 94% on room air, a respiratory rate higher than 30 breaths/min, the presence of pulmonary infiltrates on imaging higher than 50% or with a ratio of arterial partial pressure of oxygen fraction of inspired oxygen lower than 300 mm Hg [11].

Abdominal ultrasonography was performed by a single operator using Hitachi Arietta V60 using both conventional and Doppler examination. In all patients with abnormal conventional hepatic ultrasonography, we performed abdominal computer tomography scan with intravenous contrast.

Statistical analysis

The data included in this study were collected as nominal or quantitative variables. The quantitative variables were tested for normality of distribution using Kolmogorov-Smirnov test. In order to analyze independent risk factors of paraclinical and demographical distribution of COVID-19 severity we performed logistical regression analysis after univariate and multivariate analysis. We performed Fishers' exact test for categorical data and Mann-Whitney U test for continuous variables, using SPSS 19.0 software. The level of significance was set at $\alpha = 0.05$ for all tests.

Results

We aimed to include 154 patients discharged at index COVID-19 hospitalization which presented at admission or during hospitalization signs of liver injury. Forty-four patients were lost at follow-up examination and thirty-two declined to participate in a follow-up study. The flowchart of the design of the study is presented in figure 1.

We performed abdominal ultrasonography and laboratory examinations in 78 patients (mean age 45±10 years) hospitalized 6 months earlier for symptomatic COVID-19, with a male:female ratio of 1.3:1.

Thirty patients (38.46%) were discharged at index COVID-19 hospitalization with abnormal liver function tests, while the rest presented paraclinical normalization at discharge and mean duration of liver injury of approximately 7 days.

Six months later, 27 patients (34.6%) were diagnosed with abnormal liver function tests (expressed by an increased value two times ULN of ALT, AST, TB, GGT), and 74% presented with mild liver injury as per methodology inclusion criteria. The total number of patients which were diagnosed with abnormal liver function tests at 6-month follow-up included 12 patients (40%) from the total number of patients discharged at index COVID-19 hospitalization with abnormal liver function tests. Supplementary etiological investigations which could not be performed in the index COVID-19 hospitalization led to the diagnosis of viral hepatitis (B, C) infection in 3 patients and the diagnosis of autoimmune hepatitis in 2 patients.

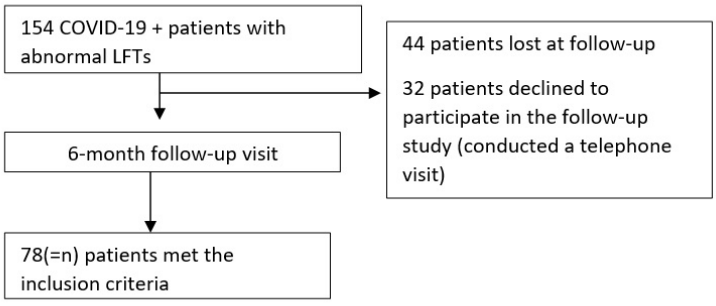

Figure 1. Study flowchart**.**

Table II. Demographics and paraclinical characteristics of 78 enrolled COVID-19 patients.

Parameter	Severity of COVID-19 at index COVID-19 hospitalization		
	Non-severe n=60	Severe n=18	p-value Student T-test
Age (years)	47.8±10.4	52.5±7.03	**0.01**
Hemoglobin (g/dL)	12.68±1.35	13.72±2.59	0.703
Platelet count (10^3/uL)	222.45±81.05	274.55±85.24	**0.02**
Leukocyte count (/uL)	5345.61±2232.78	5145.61±2132.75	0.085
ALT at index COVID-19 hospitalization (U/L)	160.22±88.13	190.15±77.17	**0.014**
ALT at 6-month follow-up (U/L)	53.22±25.02	75.15±27.05	**0.03**
AST at index COVID-19 hospitalization (U/L)	77.82±59.57	78.42±39.37	0.995
AST at 6-month follow-up (U/L)	32.80±19.44	35.80±17.22	0.941
GGT (U/L)	100.15±9.5	89.15±10.5	0.078
ALP (U/L)	81.3±33.92	77.2±17.81	0.135
TB (mg/dL)	0.71±0.14	1.05±0.25	**<0.001**
APTT (sec)	21.36±6.74	22.25±7.44	0.45
INR	1.05±0.12	1.02±0.15	0.83
Urea (mg/dL)	32.35±10.45	29.95±8.45	0.135
Creatinine (mg/dL)	0.82±0.10	0.72±0.15	0.156
Sodium (mmol/L)	134.60±3.23	132.40±3.57	0.225
Potassium (mmol/L)	4.15±0.41	4.10±0.75	0.413
Glycemia (mg/dL)	100.41±33.79	97.35±15.75	0.145
Albumin (g/L)	4.11±0.32	3.99±1.22	0.586
CRP (mg/dL)	0.67±0.31	0.82±0.71	0.048
Ferritin (ng/mL)	222.49±57.62	332.45±78.31	**0.001**
Cholesterol (mg/dL)	160.43±40.31	150.36±20.11	0.475
Triglyceride count (mg/dL)	135.1±78.14	115.4±58.24	0.128

Clinical and paraclinical characteristics are shown in Table II.

Regarding the liver injury in our research focus group (monitored at a 6-month follow-up), we obtained statistically significant differences regarding the severity of COVID-19 (groups 1 and 2) in ALT (p=0.03), TB (p<0.001) serum levels, as well as the persistence of inflammatory markers (ferritin levels, p=0.001). These results were similar to index hospitalization results, as we could conclude the persistence of liver injury and of inflammatory markers in patients with severe COVID-19 in index hospitalization.

Conventional hepatic ultrasonography was performed in all patients at the 6-month follow-up assessment included in this study by a single operator, regardless of the presence of abnormal liver function tests. Twenty patients presented with mild hepatic steatosis (grade 0-1), ten patients presented with gallbladder sludge without the presence of gallstones, two patients presented with portal venous system thrombosis and fifteen patients presented with small, round retroperitoneal or subhepatic lymphadenopathies up to 10 mm in diameter. In 10 patients, in spite of the bias of another operator, a comparison was made to the initial conventional hepatic ultrasonography at index hospitalization. The result was the presence of mild hepatic steatosis (grade 0-1) which was not described at index ultrasonography, as well as the presence of subhepatic lymphadenopathies, interpreted in the context of prolonged inflammatory status. Lymphadenopathies were described only in patients with a severe form of COVID-19 at index hospitalization.

The results of the CT scan performed in all patients with abnormal conventional hepatic ultrasonography were consistent with the ultrasonography scan, confirming the presence of steatosis, gallbladder sludge, portal venous system thrombosis or lymphadenopathies.

Comparison was made between patients in Groups 1 and 2. Patients in Group 2 had a lower platelet count (Pearson correlation test; p=0.02), a higher ALT level (Pearson test; p=0.03) and higher triglyceride count (Pearson test; p=0.01).

There was no statistically significant difference regarding the pattern of liver injury, most of the patients which were diagnosed with the persistence of liver injury (74%) presented with hepatocellular type (for both index hospitalization and the 6-month follow-up visit).

Analyzing the group of patients in which we found abnormal liver tests at 6-month follow-up, and

comparing the paraclinical results followed up in this study we discovered the presence of steatosis at imaging examination and the presence of lymphadenopathies. Patients (40%) discharged at index-hospitalization with abnormal liver function tests presented the persistence of inflammatory markers, at 6-month follow-up, in comparison with the patients without abnormal liver functions tests at discharge.

Discussion

Our study represents, as far as we know, the first follow-up review of the impact of SARS-CoV-2 associated liver injury in Romania. We followed-up the evolution of COVID-19 patients and their outcome in multidisciplinary research, being a continuation of previously published articles that outlined our work.

In our initial studies [12-14] we performed a multicenter, multidisciplinary research of COVID-19 patients with different types of severity ranging from mild form of disease to critically-ill patients, with associated liver injury. We established that the severity of liver injury was not a supplementary poor outcome risk factor in critically-ill patients and we underlined the significance of performing early etiological investigations in COVID-19 patients.

The long-term effects of COVID-19 are the key point in the research methodology of follow-up studies, as this multifaceted condition has proven its impact through multiorgan involvement. Balachandar et al. [15] in their review recommended for COVID-19 recovered patients a strict follow-up plan in order to address the repercussions of the disease.

Kunutsor et al. [16] in their meta-analysis of published studies reporting on the causality relationship between the markers of liver injury and the clinical outcome of COVID-19 patients, highlighted the different controversies regarding this pathology. Their recommendation included intensive monitoring of liver function tests during admission and after discharge, so that the therapeutic approaches could be tailored individually.

An et al. [17] in their follow-up study of liver function recovery of COVID-19 patients after discharge demonstrated that chronic liver disease, especially fatty liver may increase the risk of severe COVID-19 and helped to understand the progression of the disease and the impacts on liver function. Our study comprises the follow-up at 6 months after discharge, and highlights as well the impact of fatty liver disease and the possible clinical implications on the outcome of patients, taking into consideration the persistence of inflammatory markers and the identification of liver steatosis at conventional hepatic ultrasonography performed. We based our findings on the potential dual mechanisms of a consequence to COVID-19 severity, as well as a potential maintenance of inflammatory process of fatty liver disease. We had additional biomarkers of inflammation and liver injury, in comparison with An et al. study, in order to provide more evidence regarding prognosis.

Gan et al. [18] in their retrospective, bi-center study followed up the clinical and paraclinical characteristics of COVID-19 patients, and demonstrated the persistence of liver function tests abnormality during hospitalization and at discharge, suggesting the impact of liver injury on the prognostic outcome of patients. Our study followed-up patients who presented at discharge the lack of normalization of liver function tests, especially in patients with a severe form of COVID-19 at index hospitalization and demonstrated the persistence of liver injury in patients, even at 6 months after discharge. This could not be correlated to the known physiopathological sources of liver injury previously described in literature (as it should have been related strictly to the viral aggression and it should have been limited at duration) and could not be associated with any other pre-existing liver disease. We concluded the persistence of liver injury with a possible pathological mechanism of maintenance of inflammatory processes, related partly to fatty liver disease and partly to a prolonged process of inflammatory status. We provided complete etiological investigation results, which were possibly lacking at index COVID-19 hospitalization, due to the focus on reducing initial viral aggression. Further studies are required in order to analyze the persistence of fatty liver disease and the follow-up of inflammatory status, with the analysis of at least common inflammatory markers.

Nayagam et al. [19] in their study regarding the patterns and prediction of liver injury with persistent cholestasis in survivors of severe SARS-CoV-2 infection demonstrated that a proportion of patients with severe COVID-19 did not present normal liver function tests during follow-up examination, especially regarding gamma-glutamyl transpeptidase levels. The liver damage in COVID-19 patients could have resulted in the studied group from a direct cholangiocyte injury and the consequent bile acid accumulation induced by viral infection. Although our studied group presented mostly hepatocellular type of injury, we could associate the persistence of liver injury due to hepatocyte injury associated with ACE2 receptor, and the persistence of hepatocyte inflammatory process.

Abdominal imaging in COVID-19 patients has been a topic of interest in the search of the underlying mechanisms in the digestive involvement of SARS-CoV-2 infection.

Balaban et al. [20] in their review regarding abdominal imagistic techniques in COVID-19 patients

summarized the most frequent sonographic findings such as hepatomegaly and biliary system disease which consisted of hyperemia, intraluminal mud, pericholecystic fluid and gallbladder wall thickening, consistent with other literature studies [21,22]. The proposed mechanism in a suspicion of hepatobiliary disease was the direct viral cytopathic injury or congestive hepatopathy and the abdominal imaging technique of choice was the abdominal ultrasound. Our study summarized the findings of abdominal ultrasonography performed at 6 months after discharge in order to study the possible mechanisms of prolonged liver injury.

Gamberini et al. [23] in their follow-up study regarding the quality of life of critically-ill COVID-19 patients after Intensive Care Unit discharge demonstrated that survivors of ARDS associated with SARS-CoV-2 infection present a significant reduction on the quality of physical and psychological life. Our study summarized the clinical and paraclinical findings of critically-ill survivors discharged from the Intensive Care Unit, and the impact of liver injury on their recovery.

There are limitations to our study including the systematical investigation for liver injury etiological diagnosis at index COVID-19 hospitalization, the component of metabolic syndrome in patients diagnosed with fatty-liver disease as well as the lack of histopathological result from liver biopsies at 6-month follow-up or at index COVID-19 hospitalization (which could not be performed due to patients‘ refusal of an invasive etiological method of differential diagnosis)

Conclusions

SARS-CoV-2 associated liver injury was thought to be initially a short-term direct viral consequence, with limited impact on the prognosis of COVID-19 patients. By performing a complete clinical and paraclinical 6-month follow-up study, with a specific focus on 34.6% of patients in which we noted a persistence of liver function tests abnormality, we could analyze a possible long-term effect of SARS-CoV-2 infection over liver function and also raise awareness of liver function tests monitoring and therapeutic management in post COVID-19 patients. Long-term follow-up studies of COVID-19 multi-organ sequelae are therefore mandatory in order to improve the practice of consultant gastroenterologists.

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