Invited lecture/Scientific contribution

Diagnostic and Prognostic Analysis of Serological and Biochemical Markers in Patients with COVID-19: A Retrospective Study

Bansal Rishu [1,*], Zhamutashvili Maia [1,2], Tilante Shweta[1], Kipiani Nina[1], Badridze Nino[1], Dolmazashvili Ekaterine [1,2], Jojua Natia [1], Gognadze Tinatin[1]

1. European University, Tbilisi, Georgia
2. Infectious diseases, Aids and Clinical-Immunology Scientific-Research Center, Tbilisi, Georgia

* Correspondence: Rishu Bansal; 6990@eu.edu.ge

Abstract:
The Coronavirus Disease 2019 (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) became a challenge globally by affecting millions of people worldwide. Lung injury is the main outcome of COVID-19 infection; however, damage can occur in other organs including the liver. Currently, limited data is available that link underlying liver injury with the severe SARS-CoV-2 infection. This study aimed to investigate the changes in levels of liver enzymes in COVID-19 patients. We conducted a retrospective analysis of the medical reports of 90 admitted patients with confirmed COVID-19 in the Infectious Disease, AIDS and Clinical Immunology Research Centre, Georgia from march 2020 till August 2020. The study showed that among 90 patients with COVID-19, 24.4% (n=22) had abnormally elevated levels of liver enzymes. The presence of abnormal liver tests became more pronounced during hospitalization within 2 weeks, with 18.8% (n=17) patients having elevated alanine aminotransferase (ALT) levels, and 12.2% (n=11) patients having elevated aspartate aminotransferase (AST) levels. Considerably raised levels of liver enzymes were observed in 17.8% (n=16) older males. The hepatitis C virus antibody test and hepatitis B virus antigen test were performed in all patients and only two patients were detected with positive result of hepatitis C and hepatitis B tests. Our study indicates that patients with abnormal liver tests were at higher risk of progressing to severe COVID-19. Large-scale clinical studies are needed in the future to identify the causes of liver injury in patients with COVID-19 infection.

Keywords: COVID-19, Liver enzymes, ALT (alanine aminotransferase), AST (aspartate aminotransferase), Ag(antigen), Ab(antibody).

Citation: Bansal R, Zhamutashvili M, Tilante S, Kipiani N, Badridze N , Dolmazashvili E, Jojua N, Gognadze T. Diagnostic and Prognostic Analysis of Serological and Bio-chemical Markers in Patients with Covid-19: A retrospective study. Proceedings of Socratic Lectures. **2023**, 8; 10-13. https://doi.org/10.55295/PSL.2023.II2

1. Introduction

The Coronaviridae family includes members that express similar homology in terms of structure and pathology and includes Middle East Respiratory Syndrome (MERS-CoV), SARS-CoV, and SARS-CoV-2 that presents a global challenge since December 2019 (Schneeweiss-Gleixner, 2021). COVID-19 mainly affects the respiratory system but the involvement of other systems is of equal importance because Angiotensin-Converting Enzyme (ACE) receptors are widely spread within the body. ACE2 is present in many organs (e.g. intestine, heart, liver, kidney, nervous and muscular system) and is the main receptor for viral attachment (Nardo et al., 2021). The pathway is regulated by the host transmembrane serine protease 2 (TMPRSS2) (Nardo et al., 2021). The possible effect of preexisting disease in the liver might be important and needs further investigation of the underlying pathophysiological mechanisms leading to severe progression (Nardo et al., 2021). Most studies on COVID-19 patients showed evidence of alveolar damage (Menter et al., 2020), but liver damage has also been detected (Jothimani et al., 2020). The presence of the SARS virus in liver tissue was detected by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) but not by observation of virions by electron microscope (Anirvan et al., 2020). It could be expected that in COVID-19 the liver enzymes would be elevated since SARS-CoV-2 shares genomic similarities with SARS-CoV (Anirvan et al., 2020). Liver dysfunction can be caused by direct and indirect cytopathic effects. The direct cytopathic effect is caused by the direct interaction of SARS-CoV-2 with the host cell via ACE2 which is expressed in cholangiocytes. Surprisingly, the ACE2 expression was found higher in the bile duct than in hepatocytes which indicates that liver damage might be associated with bile duct injury and cholestatic liver injury. It was found that cholangiocytes served as a protective barrier for liver cells because of tight junctions, but the virus reduced the expression of tight junctions mRNA which in turn can leak out toxic bile contents into the hepatocellular parenchyma (Nardo et al., 2021). Transient elevation of liver enzymes can occur due to immune activation reflected in the increase of cytokines including interleukins IL-2R, IL-6, and IL-10, and tumor necrosis factor-alpha (TNF-α) also without any significant liver injury (Hamid et al., 2021). Genetic factors might be responsible for cytokine storms in response to viral specificity (Benetti et al., 2020). Positive end-expiratory pressure impeding venous return can be a reason for elevated pressure in the right atrium and can occur with or without mechanical ventilation. Drugs such as antivirals, antipyretics, and antibiotics may be associated with liver dysfunction or enzyme elevation (Vitiello et al., 2021). Older age and comorbid conditions such as hypertension, diabetes, and cardiovascular diseases render patients more susceptible to infection due to their poor immune status (Musa, 2020). Severe hepatitis has been noticed in patients with Hepatitis-B Co-infection with SARS-CoV-2 (Wu et al., 2021). Evidence from Wuhan, China showed that liver enzymes were predominantly elevated in severe patients with COVID-19. The majority of patients in this study were males with a mean age of 47 years and the majority of patients with elevated enzymes were on antiretroviral medications, therefore it was not clear whether the elevation of the liver enzymes was due to medication or a direct effect of virus. A recent study reported the presence of fever and respiratory symptoms in a COVID-19 patient who had acute anicteric hepatitis (Hamid et al., 2021). Aside from pulmonary symptoms, other clinical manifestations of the interaction of the virus with ACE2 receptors have been noted (Boregowda et al., 2020). Recent findings of anosmia and ageusia have been considered important symptoms (Boregowda et al., 2020). On the other hand, Gamma Glutamyl Transpeptidase (GGT) elevation has been reported in severe cases while Alkaline Phosphatase (ALP) levels were normal in mild to severe cases. It was suggested that outpatients without records of underlying liver disease could be managed by quarantine and routine examination of liver biomarkers is not necessary whereas, for the patients with severe progression, it was found of utmost importance (Hamid et al., 2021).It was suggested that AST, ALT, ALP, GGT, and bilirubin should be monitored on a routine basis in severe cases (Hamid et al., 2021).In some of these cases, C reactive protein, ferritin, albumin, and platelets were also found informative (Hamid et al., 2021). It was found that in order to exclude drug-related liver injury, newly founded abnormal liver parameters were managed in the same way as in the COVID-19-negative patients (Hamid et al., 2021). Increased levels of ALP and bilirubin were detected in the severe form of liver injury (Clark et al., 2021), however, the mechanism behind this is still not known. Disseminated intravascular coagulation, and thrombosis was also associated with COVID-19 (Phipps et al., 2020), but

measuring International Normalized Ratio (INR) has not been introduced as a requirement in clinical practice. However, it could be considered useful since the mild increase in INR along with hypoalbuminemia has been detected in severe COVID-19 cases (Phipps et al., 2020). D-dimer is a breakdown product of fibrin and plays a role in the activation and degradation of the coagulation pathway (Berger et al., 2020). D-dimer elevations were observed in chronic diseases (Berger et al., 2020). In Wuhan, China, assessment of coagulopathy and D-dimer was used in prognostics, decisions on the treatment, and follow-up of COVID-19 patients (Li et al., 2020). Also, it was shown that the biomarkers varied with respect to gender which was interpreted by differences in biology and lifestyle (e.g. smoking) (Haitao et al., 2020).

2. Methods

A retrospective analysis of the medical reports of 90 admitted patients with confirmed COVID-19 treated at the Infectious Disease, AIDS and Clinical Immunology Research Centre, Tbilisi, Georgia from March 2020 to August 2020 was performed. Patients in severe stages of liver injury were followed routinely for concentrations of liver biomarkers, platelets, and albumin in the blood. Biochemical parameters: concentrations of ALT and AST in blood were considered. The hepatitis C virus antibody test and hepatitis B virus antigen test was performed in all patients.

3. Results

The study showed that among 90 patients with COVID-19, 24.4% (n=22) had elevated concentrations of liver enzymes in blood at admission to the hospital (**Figure 1**) while after two weeks in the hospital, the number of patients with elevated ALT decreased to 18.8% (n=17) and the number of patients with elevated AST decreased to 12.2% (n=11). The levels of liver enzymes in the blood were considerably increased in 17.8% (n=16) of older males. One patient was found positive for hepatitis C virus antibody and one patient was found positive for hepatitis B surface antigen.

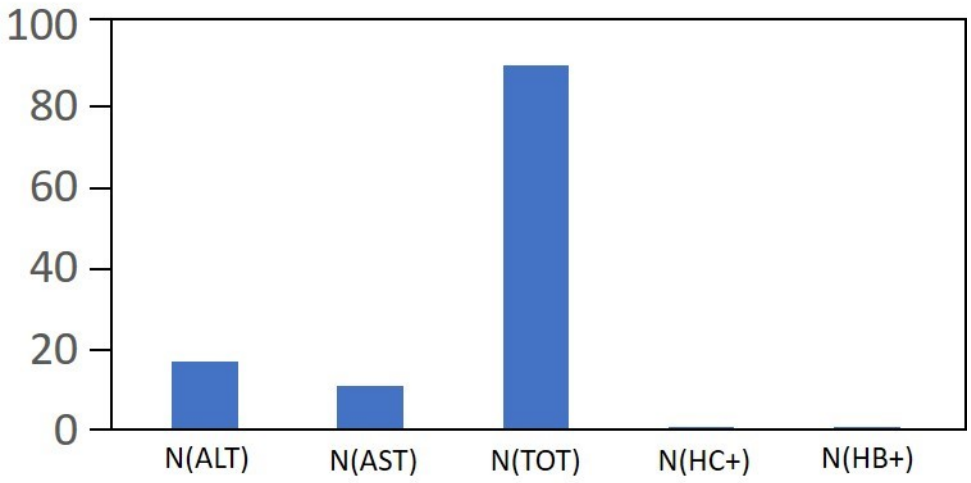

Figure 1. Numbers of patients (N) with elevated ALT and AST liver enzymes in blood and numbers of patients positive for hepatitis C virus antibody (HC+) and hepatitis B surface antigen (HB+) in the cohort of total number N(TOT) of patients with COVID-19.

3. Discussion

COVID-19 has impacted people's lives worldwide, not only biologically but also mentally and economically. Our results indicate that SARS-CoV-2 besides affecting the pulmonary system presented also with elevated liver tests (**Figure 1**). We found elevated liver enzymes mostly in elderly men which could be explained on the grounds of gender and lifestyle. Levels of biomarkers were found elevated in many chronic liver diseases (Yu et al., 2021). however, the mechanisms of association of COVID-19 with liver impairment have

not yet been explained. High mortality rates have been identified in COVID-19 patients with or without underlying liver disease. It was suggested that concentrations of ALP, ALT, AST, D-dimer, and bilirubin in all patients with severe COVID-19 would be helpful for prognostics and in decisions about the treatment. Studies in this field require further investigations (Clark et al., 2021).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Anirvan P, Bharali P, Gogoi M, et al. Liver injury in COVID-19: The hepatic aspect of the respiratory syndrome - what we know so far. World J Hepatol. 2020; 12: 1182-1197. DOI: 10.4254/wjh.v12.i12.1182
2. Benetti E, Giliberti A, Emiliozzi A, et al. Clinical and molecular characterization of COVID-19 hospitalized patients. PLoS One. 2020; 15: e0242534. DOI: 10.1371/journal.pone.0242534
3. Berger JS, Kunichoff D, Adhikari S, et al. Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. Arterioscler Thromb Vasc Biol. 2020; 40: 2539-2547. DOI: 10.1161/ATVBAHA.120.314872
4. Boregowda U, Aloysius MM, Perisetti A, et al. Serum Activity of Liver Enzymes is Associated with Higher Mortality in COVID-19: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2020; 7: 431. DOI: 10.3389/fmed.2020.00431
5. Clark R, Waters B, Stanfill AG. Elevated liver function tests in COVID-19: Causes, clinical evidence, and potential treatments. Nurse Pract. 2021; 46: 21-26. DOI: 10.1097/01.NPR.0000722316.63824.f9
6. Haitao T, Vermunt JV, Abeykoon J, et al. COVID-19 and Sex Differences: Mechanisms and Biomarkers. Mayo Clin Proc. 2020; 95: 2189-2203. DOI: 10.1016/j.mayocp.2020.07.024
7. Hamid S, Alvares da Silva MR, Burak KW, et al. WGO Guidance for the Care of Patients With COVID-19 and Liver Disease. J Clin Gastroenterol. 2021; 55:1-11. doi:10.1097/MCG.0000000000001459
8. Jothimani D, Venugopal R, Abedin MF, et al. COVID-19 and the liver. J Hepatol. 2020; 73(5): 1231-1240. DOI: 10.1016/j.jhep.2020.06.006
9. Li C, Hu B, Zhang Z, et al. D-dimer Triage for COVID-19. Acad Emerg Med. 2020; 27: 612-613. DOI: 10.1111/acem.14037
10. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology. 2020; 77: 198-209. DOI: 10.1111/his.14134
11. Musa S. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? Arab J Gastroenterol. 2020; 21: 3-8. DOI: 10.1016/j.ajg.2020.03.002
12. Nardo AD, Schneeweiss-Gleixner M, Bakail M, et al. Pathophysiological mechanisms of liver injury in COVID-19. Liver Int. 2021; 41: 20-32. DOI: 10.1111/liv.14730
13. Phipps MM, Barraza LH, LaSota ED, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. Hepatology. 2020; 72: 807-817. DOI: 10.1002/hep.31404
14. Vitiello A, La Porta R, D'Aiuto V, et al. The risks of liver injury in COVID-19 patients and pharmacological management to reduce or prevent the damage induced. Egypt Liver Journal. 2021, 11: 11. DOI: 10.1186/s43066-021-00082-y
15. Wu J, Yu J, Shi X, et al. Epidemiological and clinical characteristics of 70 cases of coronavirus disease and concomitant hepatitis B virus infection: A multicentre descriptive study. J Viral Hepat. 2021; 28: 80-88. DOI: 10.1111/jvh.13404
16. Yu D, Du Q, Yan S, et al. Liver injury in COVID-19: clinical features and treatment management. Virol J. 2021; 18: 121. DOI: 10.1186/s12985-021-01593-1