Asymptomatic COVID-19 presenting with features of mixed pattern acute liver injury in a young healthy female, a case report

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Title: Asymptomatic COVID-19 presenting with features of mixed pattern acute liver injury in a young healthy female, a case report

Authors: Phool Iqbal[1], MD, Prava Karki[1],MD, Wael Abdelmottaleb[1],MD, Yamama Al-Khazraji[1], MD, Ahmed Mirza[1], MD, Kulsum Madani[1], MD, Farhan Ahmed[1], MD, Shoaib Nawaz[2], MD, Dr. Muhammad Bilal Jamshaid[3], MD, Dr. Quesada Mata, Fernando[1], MD.

Affiliation:

Department of internal medicine New York Medical College/Metropolitan Hospital Center[1]

Department of Anesthesia New York Medical College/Metropolitan Hospital Center[2]

Department of Rheumatology, Hamad Medical Corporation, Qatar

Authors email:

1- Dr. Phool Iqbal, MD

Email: dr.phooliqbal89@gmail.com

2- Dr. Prava Karki, MD New York City Health and Hospitals Metropolitan

Email: prava.karki3@gmail.com

3- Dr. Wael Abdelmottaleb, MD

Email: W.abdelmottaleb@gmail.com

4- Dr. Yamama Al-Khazraji, MD

Email: Yamama.alkhazraji82008@gmail.com

5- Dr. Ahmed Mirza, MD

Email: ahmed.fawad@outlook.com

6- Dr. Kulsum Madani, MD

Email: kulsum.madani1@gmail.com

7- Dr. Farhan Ahmed, MD

Email: ahmedfarhan.md@gmail.com

8- Dr. Shoaib Nawaz, MD

Email: shoaibnawaz89@hotmail.com

9- Muhammad Bilal Jamshaid, MD

Email: drbilaljamshaid@gmail.com

10- Dr. Fernando Quesada Mata, MD

Email: fernando.qmat@gmail.com

Abstract:

COVID-19 associated severe acute liver injury in a young healthy patient has not been reported much in the literature. And currently, there are no standard management guidelines. We want to report a case of acute liver injury of mixed pattern in a young healthy female with asymptomatic COVID-19 infection. She presented with abdominal pain, nausea, vomiting and yellowish discoloration of her skin. Further laboratory investigations revealed mixed pattern liver injury with highly raised liver enzymes. She was managed with N-acetyl cysteine protocol and monitoring of her liver enzymes. Other causes of acute liver injury were ruled out. She remained stable during her hospital stay and follow up. Our aim is to highlight the significance of acute liver injury in COVID 19 patients that may lead to fatal outcomes if not managed and monitored accordingly.

Introduction:

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 RNA commonly affects the respiratory system and has extra-pulmonary manifestations [1]. The prevalence of COVID-19-induced liver injury is reported as 19% (range: 1%-53%) [2] and may vary from mild transaminitis to acute liver failure and poor prognosis [3, 4]. The most likely proposed mechanisms of acute liver injury in COVID-19 patients include drug-induced liver injury, direct cytotoxicity, hypoxic liver injury, and worsening of pre-existing metabolic liver disease [2]. We report a case of asymptomatic COVID-19 infection in a young, healthy female who presented with abdominal pain associated with nausea and vomiting and was found to have a mixed pattern of acute liver injury.

Key words: COVID-19, Liver Injury, acute hepatitis, abnormal liver enzymes, N-acetyl cysteine (NAC)

Case presentation:

A 29-year-old female without any past medical history presented to the emergency department (E.D.) with six days of nausea, vomiting containing only food particles, and non-radiating right upper quadrant abdominal pain. She reported generalized fatigue, yellowish discoloration of her skin, eyes, and dark urine for the last three days. She took acetaminophen for one day, a total of 1gm, for her fatigue. There was no history of fever, night sweats, joint pains, rash, drug/alcohol abuse, sick contact, or recent travel. She has been up to date with her vaccinations, including the COVID-19 vaccine. Family history was also unremarkable for any autoimmune diseases or malignancies. Initial vitals on presentation were stable, and physical examination was remarkable for scleral and skin icterus and right upper quadrant tenderness on deep palpation without organomegaly.

Blood investigations showed normal complete blood counts, significantly elevated transaminases, bilirubin, and INR ratio, as mentioned in Table 1. Upon screening, she tested positive for COVID-19 and did not complain of respiratory symptoms. Her serum acetaminophen level was normal.

Abdominal ultrasound (USG) was unremarkable for any portal vein (P.V.) thrombosis, liver structure abnormality, common bile duct, or gallstones. She was managed with fluid resuscitation with 1.5L of normal saline and was urgently started on N-acetyl cysteine (NAC) protocol for acute liver injury after the consultation and recommendations of the gastrointestinal (G.I.) team. Abdomen and pelvis C.T. scans were unremarkable for hepatobiliary pathology. An extensive workup for the possible causes like portal vein thrombosis, viral hepatitis (hepatitis A, B, C, E, cytomegalovirus, Epstein-Barr, HIV, Parvovirus, and HSV), hemochromatosis (serum ferritin and iron studies), Wilson's disease (serum ceruloplasmin levels), alpha-1 antitrypsin deficiency and autoimmune diseases like autoimmune hepatitis (ANA, anti-smooth muscle and anti–liver-kidney microsomal antibody or LKM antibody and primary biliary cholangitis (antimitochondrial Abs) was performed and was unremarkable. Therefore, COVID-19-induced acute liver injury was considered the primary diagnosis of her presentation. The patient remained stable during her hospital stay, and her liver enzymes trended down significantly, as mentioned in table 1, with improvement in her skin and urine color. She was able to tolerate food without nausea or vomiting and was discharged with follow-up as an outpatient with the primary care physician and G.I. team. She remained stable during her follow-up post-discharge.

Discussion:

COVID-19 infection caused by SARS-COV-2 primarily affects the respiratory system and commonly presents with symptoms of upper respiratory tract infection like fever, cough, sore throat, headache, and myalgias; however, in 15% of the severe cases of COVID-19 infection, it can deteriorate to acute respiratory distress syndrome and multi-organ failure [2, 5]. One of the commonly reported complications includes acute liver injury with a prevalence of 19% (range: 1%-53%) [2, 6], and the clinical manifestation can range from being asymptomatic to acute liver failure with signs of decompensation [4]. The severity of liver damage usually correlates with the severity of COVID-19 infection[7], underlying chronic liver disease like alcohol-related liver disease, nonalcoholic fatty liver disease, cirrhosis, autoimmune hepatitis, chronic viral hepatitis, and hepatocellular carcinoma [4, 8-10]. The underlying pathophysiology of COVID-19-induced liver injury is not clear; however, the proposed mechanism is related to direct cytopathic viral effect, cytokine storm leading to immune-mediated hepatitis, hypoxic injury, drug-induced liver toxicity, and underlying chronic liver diseases [2, 3, 7, 8] as mentioned in figure:1. It is also well known that SARS-Cov-2 attaches to ACE2 receptor found in pulmonary, biliary ad hepatic epithelia. Furthermore, detecting the virus in stools suggests universal hepatic involvement via first pass effect irrespective of the elevation of liver or biliary enzymes [7]. Our patient presented with nausea, vomiting, clinically evident jaundice, direct hyperbilirubinemia, and high levels of transaminases, as mentioned in table:1. Considering her raised liver enzymes, she was commenced on NAC protocol after consulting and getting recommendations from G.I. service.

Meanwhile, other possible causes of acute liver injury were worked up and ruled out, as mentioned in the case presentation. The only remarkable finding was COVID-19 infection. Upon literature review, a recent meta-analysis by Yang et al. reported that patients with gastrointestinal symptoms had higher AST and ALT than those without the G.I. symptoms, as seen in our case[7]. The most common pattern of liver damage in COVID-19 patients is hepatocellular injury. However, the cholestatic and mixed pattern is also seen, especially due to certain drugs like systemic corticosteroids, antivirals like remdesivir, immunoregulatory factors like Tocilizumab and antibiotics used in COVID-19 management [6, 7]. The mixed pattern of liver injury and severity of liver damage seen in our patient without any chronic liver disease, triggering drug or severe

COVID 19 infection has not been reported in the literature. We managed our patient initially with fluid resuscitation, but it did not improve her liver functions, and she was started on NAC protocol. A meta-analysis by Walayat et al. reported that early NAC administration has some beneficial role in non-acetaminophen liver injuries, and American Association for the Study of Liver Diseases guidelines also support this notion [11]. There are no standard guidelines, and various management approaches have been discussed in the literature based on expert opinion and individual case-based clinical judgment [12]. We created an algorithm to summarize those proposals mentioned in the literature[13, 14], as in figure 2. We monitored our patient during her hospital stay and she improved gradually without complications. She was discharged and remained stable during her follow-up.

Conclusion:

COVID-19-induced liver injury is quite common; however, based on the severity of liver damage, it needs thorough investigations and workup to rule out other possible triggers to avoid fatal outcomes and mortality. The literature currently lacks standard treatment guidelines, and each case is managed on individual case-based scenarios and expert opinions. Therefore, reporting such cases with their respective management approach is of utmost importance to guide the medical community. Further studies are required to create standard guidelines for COVID-19-induced liver damage.

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Table 1: Blood investigations trend for complete blood counts, Alk phosphatase, transaminases, bilirubin, and INR ratio.

	Day 1	***Day 2***	***Day 3***	***Day 4***	***Normal values***
Hb	14	13.9	12.7	12.1	12 - 16 g/dl
WBCs	6.34	6.04	5.16	6.29	4.3 - 11x10^3 /microlitre
Platelets	338	394	361	342	150 – 450 x10^3/microlitre
MCV	83.5	82.9	83.6	83.4	82 - 100 FL
Alk phosphatase	274U/L	237U/L	216U/L	206U/L	35-104U/L
AST	1954	1209	953	765	0 - 32 U/L
ALT	2821	2140	1552	1307	0 - 31 U/L
Bilirubin	8.1	7.8	7.1	5.4	0 - 1.2 mg/dl
Direct Bilirubin	5.5	5	4.5	3.1	0 – 0.3 mg/dl
INR	1.7	1.7	1.4	1.3	0.9 – 1.1 ratio
PT	19.4	19.9	16.7	15.6	9.4 – 12.5 seconds
Creatinine	0.5	0.5	0.7	0.6	0.7-0.9
Serum sodium	138	136	139	136	136-145
Serum potassium	3.6	3.8	3.6	3.7	3.5-5.1

Figure: 1, POSSIBLE MECHANISMS OF LIVER INJURY IN COVID 19

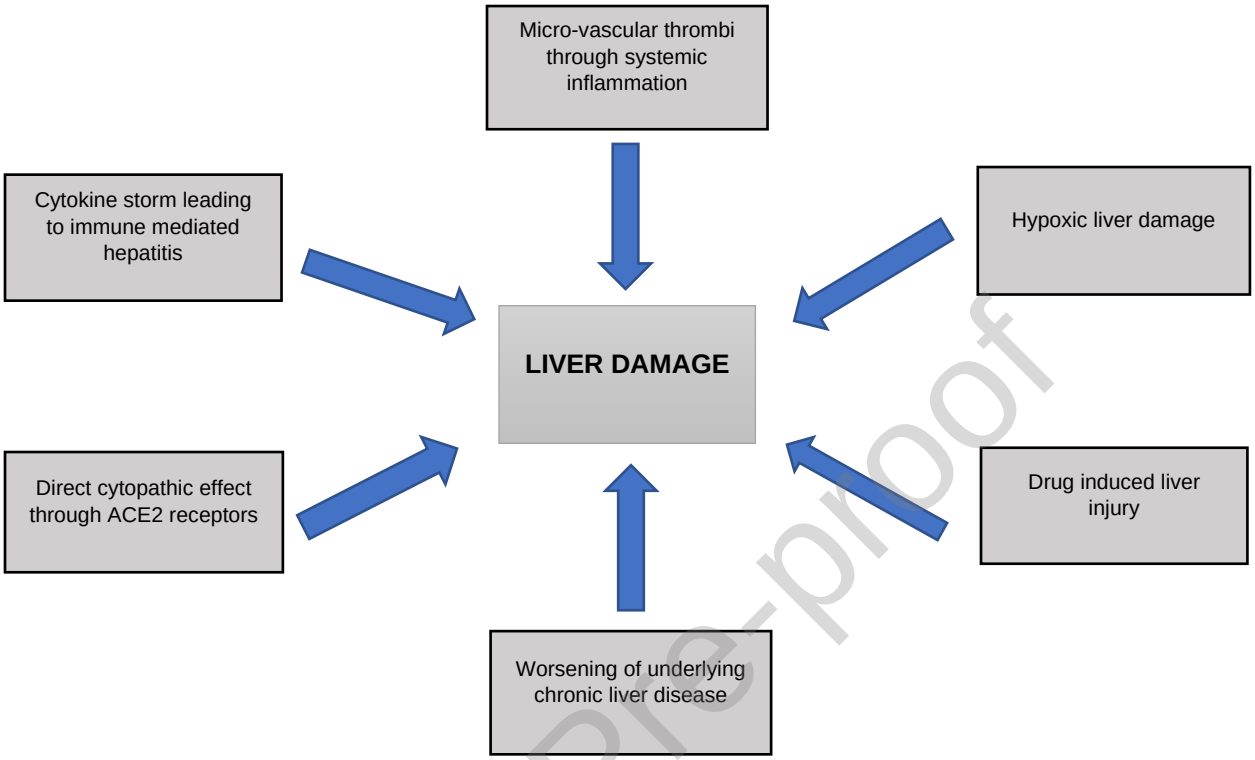
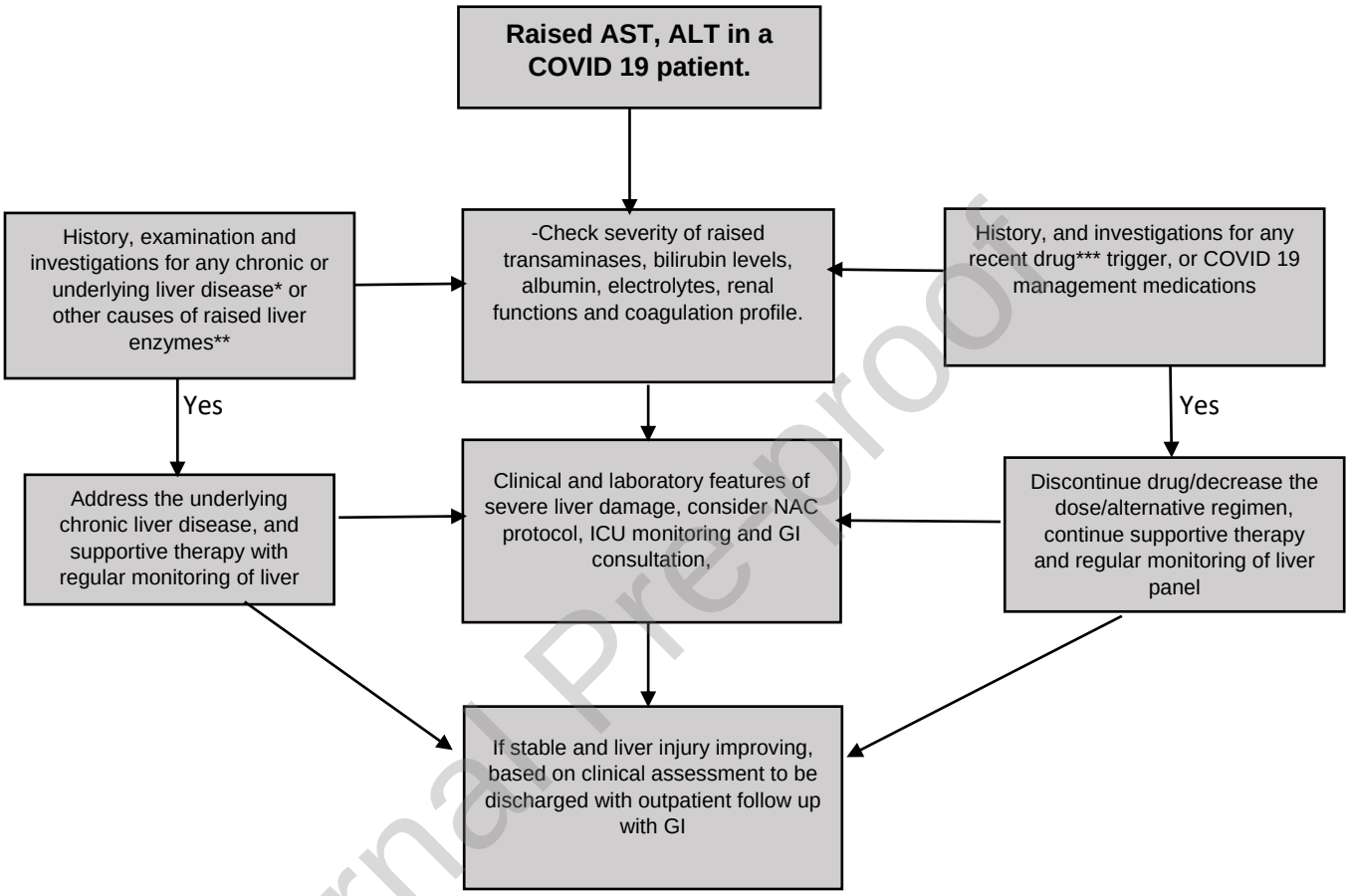


Figure: 2, Proposed algorithm based on literature review:



***Chronic liver diseases and other underlying liver diseases**: HCV, HBV, alcoholic liver, hemochromatosis, Non-alcoholic fatty liver disease, Wilson's disease, alpha-1 anti-trypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, auto-immune hepatitis etc.

****Other cause of raised liver enzymes other than liver injury:** myositis (especially glutamic oxalacetic transaminase > ALT), cardiac injury, ischemia, and cytokine release syndrome [12].

*****Likely causes of drug induced liver damage in COVID 19 patient:** anti-viral drugs like Remdesevir, Lopinavir/Ritonavir, corticosteroids, Oseltamivir, Tocilizumab, tofacitinib, Acetaminophen, SARS-Cov-2 Vaccination, antibiotics like azithromycin, anti-malarial like hydroxychloroquine [14].