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Coronavirus disease (COVID-19) in hepatic patients

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Abstract

A new coronavirus (severe acute respiratory syndrome) (SARS-CoV-2) epidemic initially began in Wuhan, China, in December 2019, which became international harm to public life. Globally the count of reported patients of COVID-19 (SARS-CoV-2) from 31st December 2019 to 14th April 2020 has achieved 1 873 265 cases, which include 118 854 fatalities**.** Many of the COVID-19 cases seem to be mild and rapidly improved, however, the infection can be terminal, with an incidence of deaths about 3 percent. Pulmonary disease was found to be the main injury done via the coronavirus two disease (SARS-CoV-2). Furthermore, hepatic damage was documented to exist in extremely ill patients. Likewise, multiple pieces of research found that hepatic injury became widespread in cases diagnosed with another two more serious coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) and correlated to the intensity and poor outcome of the infection.

Keywords: COVID-19, Chronic liver disease, Management**.**

Introduction:

Coronavirus (COVs) is an RNA virus that is commonly distributed in primates, rodents, pigs, cats, dogs, and several species. Seven coronavirus strains thought to produce human illness, four of them (HCoV-NL63, HCoV-229E, HCoV-OC43 and, HCoV-HKU1) produce pulmonary disease in immunosuppressed persons, children, and elders. **(1)** The other three were the more harmful coronaviruses, which include the severe acute respiratory syndrome coronavirus (SARS-CoV), the Middle East respiratory syndrome coronavirus (MERS-CoV), and the novel coronavirus (SARS-CoV-2). The last three pathogens may produce pulmonary, digestive, hepaticological and neurological illness, and can produce acute respiratory distress syndrome (ARDS), organ failure as well as a collapse in extremely ill patients. Multiple research found that SARS-CoV, MERS-CoV, and SARS-CoV2 affected cases can represent various forms of hepatic damage. **(2,3)**

COVID-19 infection mostly presented with fever, tiredness, dry cough, and decreased white blood cell count. Several cases may present with dyspnoea, generalized body pain, rhinitis, and dysphagia. The virus can also induce nausea, vomiting, and diarrhea. **(4)** The course of the infection may be, worsen and cause

ARDS, sepsis, acidosis, and often loss of life. **(5)** While in the majority of patients the course of infection remains mild. Hypertensive, diabetics, older patients, and those with coronary heart disease had been considered to have an increased death rate. **(6,7)**

Hepatic affection with COVID-19:

Hepatic injury in COVID-19 infected persons may be produced primarily when the virus attacks the hepatic tissue. About 2-10 percent of COVID-19 infected persons complain from diarrhea, SARS-CoV-2 RNA was found in feces and serum**(8)**, which indicates the hepatic affection by the virus. Either SARS-CoV-2 or SARS-COV affects the target cell by combining with the angiotensin-converting enzyme 2 (ACE-2) receptor. **(9)**

Sever long-standing hepatic problems as cirrhosis was considered a risk factor for COVID-19 disease, it is attributed to the immune deficiency state of cirrhotic individuals. **(10)** In cases with severe COVID-19 infection, symptoms of liver damage can be developed**(7)**, with the possibility of liver failure or the occurrence of acute hepatitis. **(11)**

Current COVID-19 researches found that the frequency of hepatic damage varied between 14.8 percent to 53 percent, it is primarily due to elevation of ALT/AST results associated with a mild increase of bilirubin results. **(5)** Reduced albumin levels may be detected in severe cases. **(12)** The incidence of hepatic damage in severely ill COVID-19 persons has been substantially greater than that in mildly ill persons. **(5,13)** In extremely ill COVID-19 case, single research recorded that the results of ALT and AST elevated to 7590 U/L and 1445 U/L, respectively. **(12)** Gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) were diagnostic biomarkers for cholangiocyte injury. GGT and ALP were elevated in (54%) and (1·8%) of 56 COVID-19 patients during hospitalization**. (14)**

Postmortem biopsies were recently performed and found that moderate fatty infiltration and mild portal inflammation, suggesting that the lesions caused by SARS-CoV-2 disease or hepatic damage cause by several agents **(15)** as lopinavir/ritonavir, that acted as antiviral therapy for the management of SARS-CoV-2 disease. **(16)**

COVID- 19 and hepatitis viruses:

Hepatitis viruses infected patients have an elevated risk of serious COVID-19 disease, particularly if associated with medical problems like renal failure, coronary heart disease, and uncontrolled blood sugar**. (17)**

Sofosbuvir plus daclatasvir is the most effective pan-genotyping antiviral therapy against hepatitis C virus infection (HCV), several studies suggest that sofosbuvir combined with other DAAs may inhibit COVID 19 replication. **(18)**

COVID- 19 and fatty liver disease:

Persons with fat infiltration of hepatic tissue might complain from systemic problems like hyperglycemia, weight gain, hypertension, hypercholesterolemia. So they may be at elevated risk of serious COVID-19 disease. **(17)**

Diagnostic procedures:

1) Endoscopies: Endoscopic procedures in COVID-19 patients increase SARS-CoV-2 spread. On esophago-gastric-duedenoscopy or endoscopic-retrograde-cholangiography, dissemination of the

infection could happen. Passage of the virus in the feces helps in the spread of the infection on lower endoscopy. So the performance of endoscopies in COVID-19 individuals must be restricted to special situations like internal hemorrhage, infectious cholangitis, or any serious problems. **(19)**

2)liver biopsy: Suggestions have firmly relied on the COVID-19 liability and the personal recommendations for histological evaluation. Histological findings in COVID-19 will mask the etiology of hepatic disease. This procedure can play a role in the spread of the infection**. (19)**

Outpatient treatment of hepatic persons throughout COVID-19 outbreak:

Tobias et al recommend the following**(19)**:

A)Patients with compensated liver disease

- Visiting specialized centers Could be adjourned.
- Make the most of primary care services through telephone.
- The frequent chemical analysis may be carried out regionally via health care physicians, and the rate of its performance requires proper thinking of the personal risk-benefit ratio.
- Patients with fatty liver disease may suffer from metabolic comorbidities leading to a serious course of the disease.
- Individuals suffering from immune-related hepatic conditions should be advised to decrease the therapeutic dose of the medications particularly if they use (e.g. drugs lead to a decrease of the lymphocytic count or bacterial/fungal infection in patients with serious SARS-CoV-2).
- Immunization against Streptococcus pneumonia and Influenza.
- Evaluation of hepatic focal lesions and esophageal varcies may be postponed in cirrhotic persons with good liver functions. We can also use platelet count to evaluate the risk of esophageal varicose veins. **(20)**
- Avoid taking a large dose of acetaminophen.
- Avoid administration of non-steroidal anti-inflammatory agents in cirrhotic persons associated with elevated portal pressure. **(21)**

B) Persons with impaired hepatic function

- Management can be performed in conjunction with protocols with limited access to healthcare members, through telephone and primary care services whenever applicable to prevent hospitalization.
- Treatment of cirrhotic problems like elevated portal pressure, accumulation of peritoneal fluid, neurological complication, bacterial peritonitis can be persisted.
- Lists of hepatic transplantation can be limited to cases with a bad outcome.
- Decreasing the inpatient hepatic transplantation monitoring system to the needed individuals to decrease the duration of hospitalization.
- Immunization against Streptococcus pneumonia and Influenza.
- Drugs used to avoid the occurrence of bacterial peritonitis and neurological complications must be strictly monitored to decrease hospitalization.
- Examination for COVID-19 virus in cases with hepatic dysfunction.

C)Evaluation of individuals prepared for transplantation:

- COVID-19 must be examined in each donor and recipient before the procedure.

- The possibility of SARS-CoV-2 infection must be involved in an agreement for any transplant-related methods of intervention.

D)Monitoring of post-transplantation situations

- Management can be performed in conjunction with protocols with limited access to healthcare members, through telephone and primary care services whenever applicable to prevent hospitalization.
- Immunization against Streptococcus pneumonia and Influenza.
- Reduction of immunosuppressive therapy during using (e.g. drugs lead to the decrease of the lymphocytic count or bacterial/fungal infection in patients with serious SARS-CoV-2). **(22)**

E) Persons with hepatoma

- Management can be performed in conjunction with protocols involving ongoing systemic therapy and assessment for hepatic transplantation, with limited access to healthcare members, through telephone and primary care services whenever applicable to prevent hospitalization.
- Local treatment must be delayed and immune-suppressed drugs may be temporarily removed.
- In SARS-CoV-2 infected patients, hospitalization is required.

Inpatient management of hepatic cases throughout the SARS-CoV-2 outbreak:

Individuals with longstanding hepatic conditions may need hospitalization and treatment of hepatic dysfunction, and any problems particularly when there are medical comorbidities like elevated blood pressure, hyperglycemia, overweight, cirrhotic liver, hepatic tumor or after transplantation condition. Basic measures should be used to avoid COVID-19 contamination. **(19)**

Treatment considerations for COVID-19:

Currently, no agents confirmed for COVID-19 treatment, many medications have been investigated during the current period**. (23)**

Remdesivir works as an adenosine-analog that trigger RNA string destruction. **(24)** Recently it decreased the SARS-CoV-2 extraction in the animal model**(25)** and reduced the intensity of the illness of the associated MERS-CoV-disease in a non-human primate. **(26)** Multiple studies have indicated that it is clinically successful in COVID-19 cases. **(27,28)**

Ritonavir/lopinavir had activity against COVID-19 in animals, a recent medical study in serious SARS-CoV2 cases
found no benefit relative to no medicat ion in *vivo*.**(29)**

Chloroquine phosphate or hydroxychloroquine has activity on COVID-19 in *vitro* through interacting with the ACE2 receptor-induced apoptosis and we can use it in the management of serious illness cases as a single therapy or beside azithromycin. **(25,30, 31)**

Persons with longstanding hepatic problems, we should think about the potential complications that may occur, as the action between anti-COVID-19 agents and immunosuppressants, where its dose should be strictly controlled. Furthermore, cases with hepatic dysfunction are at increased risk of medication toxicity (Table 1). **(19)**

We should note that any of the above-mentioned medications are being investigated. Nevertheless, the rapid induction of the treatment inhibits the intensity of the illness. **(19)**

Drug	Considerations for patients with liver diseases or after liver transplantation
Remdesivir	• Medication interactions not experienced. • (elevated ALT) may occur.
Chloroquine/hydroxychloroquine ± azithromycin	• Not used with deficiency of G6PD. • A strict follow up of the immunosuppressant dose is indicated. • Elevated ALT levels do not commonly occur with Hydroxychloroquine.
Lopinavir/ritonavir	• Immunosuppressants must not be given in combination with it, and a strict follow up if is needed. • Lopinavir related hepatic injuries were not common. • Depending on its action on chronic hepatitis C persons, it is not used in persons with impaired liver function.
Sofosbuvir ± *ribavirin*	• Ribavirin can induce hemolysis.

Table 1: the possible drug interaction that may occur with anti-COVIDE-19 treatment (19)

Reference

1.Wong G, Shi W, Su S, et al (2016): Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol; 24(6): 490-02.

2. Peiris J, Lai ST, Poon L, et al (2003): Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet; 361(9366): 1319-25.

3. Zhang D, Zhu NA, Wang W, et al (2020): A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine; 382(8): 727-33.

4. Guan W, Ni Z, Hu Y, et al (2020): Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv.

5. Huang C, Wang Y, Li X, et al (2020): Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet; 395(10223): 497-06.

6. Zhou X, Zhang B, Qiu Y, et al (2020): Clinical characteristics of 82 death cases with COVID-19. medRxiv.

7. Yang X, Yu Y, Xu J, et al (2020): Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single- centered, retrospective, observational study. Lancet Respir Med.

8. Yeo C, Kaushal S, Yeo D (2020): Enteric involvement of coronaviruses: is faecal&oral transmission of SARS-CoV-2 possible? The Lancet Gastroenterol&Hepatol; 5: 335-37.

9. Wang D, Hu BO, Hu C, et al (2020): Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA.

10. Albillos A, Lario M, Álvarez-Mon M (2014): Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. Journal of Hepatol; 61: 1385-96.

11. Schütte A, Ciesek S, Wedemeyer H, Lange CM (2019): Influenza virus infection as precipitating event of acute-on-chronic liver failure. Journal of Hepatol; 70: 797-99.

12. Chen N, Zhou M, Dong X, et al (2020): Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet; 395(10223): 507-13.

13. Cai Q, Huang D, Ou P, et al (2020): COVID-19 in a Designated Infectious Diseases HospitalOutside Hubei Province, China. medRxiv.

14. Chai X, Hu L, Zhang Y, et al (2020): Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv.

15. Shi H, Han X, Jiang N, et al (2020): Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis.

16. Fan Z, Chen L, Jun LI, et al (2020): Clinical features of COVID-19- related liver damage. medRxiv.

17. William C, Isaac B (2020): Canada's source for HIV and hepatitis C information; CATIE News.

18. Greg J (2020): Hepatitis C blog deals with all the issues associated with hepatitis C**.** Rise again; Hepatitis C blog**.**

19. Tobias B, Philip N N, Mario U M, et al (2020): Care of patients with liver disease during the COVID-19 pandemic; EASL-ESCMID Position Paper.

20. Maurice JB, Brodkin E, Arnold F, et al (2016): Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. Journal of Hepatol; 65: 899-05.

21. Chandok N, Watt KDS (2010): Pain Management in the Cirrhotic Patient: The Clinical Challenge. Mayo Clinic Proceedings; 85: 451-58.

22. Zhu L, Yang J, Guan H, et al (2020): Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. American Journal of Transplantation.

23. Harrison C (2020): Coronavirus puts drug repurposing on the fast track; EASL-ESCMID Position Paper.

24. Warren TK, Jordan R, Soloveva V, et al (2016): Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature; 531: 381-85.

25. Wang M, Cao R, Zhang L, et al (2020): Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus in vitro. Cell Research; 30: 269-71

26. Feldmann F, Cronin J, Jordan R, et al (2020): Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proceedings of the National Academy of Sciences.

27. Holshue ML, DeBolt C, Lindquist S, et al (2020): First Case of 2019 Novel Coronavirus in the United States. New England Journal of Medicine; 382: 929-36.

28. Sheahan TP, Sims AC, Leist SR, et al (2020): Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature Communications; 11: 222.

29. Cao B, Wang Y, Wen D, et al (2020): A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. New England Journal of Medicine.

30. Li G, De Clercq E (2020): Therapeutic options for the 2019 novel coronavirus. Nat Rev Drug Discov; 19: 149-50.

31. Gautret P, Lagier JC, Parola P, et al (2020): Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents.