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Research Article

COVID-19 and Liver Disease

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Abstract

The coronavirus disease 2019 (COVID-19) was first notify to WHO on December 2019 by china after its eruption in Wuhan, subsequently now it has been noticed globally and WHO Declares it as pandemic on 11-3-2020. Respiratory manifestations are predominant feature of COVID-19, but in severe illness and critical patients multi-organ involvement occurs and results in dismal prognosis. Liver patients are also at great risk of worsening of underlying compensated condition and can develop acute decompensation or exacerbation of liver disease with high morbidity and mortality especially in immunosuppressed state due to advanced liver diseases and some patients on immunosuppressive drugs; e.g. autoimmune liver disease and post liver transplantation. This mini review is about the brief summary of the impact of COVID19 infection on patients of liver diseases and management of COVID in liver patients.

Keywords: Liver Cirrhosis; COVID-19; SARS-COV2; Management

Introduction

There are seven different strains of corona virus, 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS), SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS) and SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19). COVID-19 is a beta-coronavirus - same subgenus as SARS virus as well as several bat corona viruses, is a non-segmented, enveloped RNA virus [1]. The early major epidemic in humans of severe acute respiratory syndrome (SARS) caused by coronaviruses happened in 2003 with ~10% mortality. Later this was overshadowed by Middle-East respiratory syndrome (MERS) in middle-east region (2007) and had higher rates of death (~34%) [2] Spike protein of SARS COV2 is antigenic. Mutations in Receptor Binding Domain (RBD) of SARS-Cov-2 (2019) turns it deadlier than earlier SARS-Cov (2003) [3,4]. Two major strains of COVID 19 are defined: L Strain: 70% cases, major type more aggressive and S Strain: 30% cases, minor type, less virulent. Significance of this likely that in some areas less virulence with similar demographic profiles [4,5]. The current ongoing global outbreak of SARS-COV2 is largest pandemic of the current decade. SARS-COV2 have varied manifestations, ranging from asymptomatic carriers to critical ill multiple organ dysfunction that can lead to death. Old age patients with chronic diseases have more serious infections (HTN, DM, CKD, etc.) than young age patients without comorbidities [6]. Critical illness and multiple organ involvement is a result of systemic inflammation via immune dysfunction and cytokine storm with manifestations of macrophage activation syndrome (hepatic dysfunction, hyperferritinaemia, and DIC (disseminated intravascular coagulation) [7].

Mechanism of SARS-COV2 infection and injury

The angiotensin-converting enzyme(ACE2) 2 is a key receptor for the SARS-CoV-2 viral entry which is expressed by type II alveolar cells (in lungs), cholangiocytes in liver and enterocytes in intestine, proximal tubule cells of kidney and myocardial cells. This indicates the possibility of extrapulmonary sites as reservoir for vi-

ral replication [8,9]. Bystander Hepatitis as a result of SIRS storm, produced by COVID 19 infection. Impaired innate immunity, manifested by derailed functional diversity of macrophages.

Over activation of T cells, increase of Th17 and high cytotoxicity of CD8 T cells. One recent study suggesting that an altered immune response likely the main cause of pulmonary injury and suggesting possible protective role of early immunosuppression in the treatment [10].

Most cases of COVID-19 appear to be mild, with the most common symptoms being fever (83% - 98%), cough (46% - 82%), myalgia or fatigue (11% - 44%) and shortness of breath (31%) [11,12]. The incubation period for SARS-CoV-2 appears to average 5.2 days but may range from 2 to 14 days, and potential asymptomatic infection has been reported [12,13]. The spectrum of symptomatic infection ranges from mild to critical; most infections are mild and are not severe. In a report from the Chinese Center for Disease Control and Prevention that included approximately 44,500 confirmed infections with an estimation of disease severity found 81% patients with Mild (no or mild pneumonia), 14% cases were of Severe disease (e.g., with dyspnea, hypoxia, or > 50 percent lung involvement on imaging within 24 to 48 hours) and 5% were of Critical disease (e.g., with respiratory failure, shock, or multiorgan dysfunction). The overall case fatality rate was 2.3% with no deaths were seen in noncritical cases.

Risk factors for more severe illness are old age, chronic medical conditions such as diabetes, chronic lung, liver and kidney disease and cardiovascular disease [6,11,12]. Leukopenia, leukocytosis, and lymphopenia have been reported. Lymphopenia appears most common > 80%. Increase CRP, D Dimer, LDH and ferritin levels are common. Increase AST/ALT/T bilirubin, Increase IL6. On admission, many patients with pneumonia have normal serum procalcitonin levels; however, in those requiring ICU care, they are more likely to be elevated. High D-dimer levels and more severe lymphopenia have been associated with mortality.

Patients with NASH, at high risk of severe COVID 19, due to associated comorbidities. Intensive care admissions are required in 5% to 26.1% in various studies and 4% to 15%. COVID-19 patients presented with GI symptoms, mostly in elderly with multiple comorbid condition, more chance of being on mechanical ventilation, having elevated ESR, and at more risk of death compared patients reported without diarrhea. Diarrhoea reported in up to 10 - 37% of infected patients, 25% abdominal pain, 16% can present with GI symptoms only [14]. Meta-analysis of 16 studies, more than 4200 COVID-19 patients [15] showed that Virus RNA was detected in stool samples from 48% patients. 70% patients remain positive for stool RNA even after respiratory swab became negative. Thus, attention to preventing fecooral transmission of COVID-19 is crucial, especially in reinfection and community transmission [16]. Stool should be tested for COVID 19, even if not symptomatic, in prospective FMT donor in currant scenario [17].

Liver injury in COVID-19

The most frequent abnormality in liver function tests in COVID-19 includes raised transaminases, which are usually mild and transitory. More severe elevation of AST and ALT levels are noted in patients with severe COVID-19, likely due to collateral damage. Jaundice is rare in patients with no pre-existing liver disease. The post-mortem liver biopsy from a patient with COVID-19 showed only microvesicular steatosis, which is a common finding in sepsis [18,20], liver injury in COVID 19 unlikely to be due to direct cytopathic damage.

Overall, the incidence of elevated serum liver biochemistries in hospitalized patients with COVID-19, primarily elevated AST and ALT, and slightly elevated bilirubin, ranges from 14% to 53% [12,19]. Death in COVID 19 with liver injury 58.06% - 78%. The albumin is decreased in severe cases and the level of albumin is around 26.3 - 30.9 g/L. Several studies have shown different degrees of elevated serum liver biochemistries in COVID-19 patients, mainly indicated by abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels accompanied by slightly elevated total bilirubin (TB) levels. In fact, the incidence of elevated ALT and AST ranged from 2.5% - 50.0% to 2.5% - 61.1% respectively [18,19]. With regard to TB, studies have reported increased levels in 0% - 35.3% of cases. Relevant elevations of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) levels have not been reported in most studies [20-22]. Male sex, expectoration, myalgia, severe COVID condition and decreased albumin were associated with poor improvement [23]. Increased liver enzymes are observed more commonly in males and are higher in more severe cases than in milder cases. Low albumin is a maker of severe infection and poor prognosis [23].

The development of severe hepatitis leading to acute liver failure is rare and it should be attributed to SARS-COV2 only after thorough evaluation of more common causes including drugs

and Hepatotrophic viral infections. The mechanism of liver injury is highly variable and natural course of disease is poorly defined. Liver injury may result from direct cytotoxicity due to active viral replication in hepatic cells through binding of SARS-CoV-2 to ACE2 expressed abundantly in the liver and biliary epithelial cells. The most common mechanism is probably by-stander hepatitis as a result of severe inflammatory response following COVID-19 infection as the inflammation biomarkers including C reactive protein, serum ferritin, LDH, D-dimer, IL-6, IL-2, were significant elevated in severe patients with COVID-19 [24]. Other possible mechanisms include hypoxic hepatitis due to anoxia related to respiratory failure in severe cases; Drug induced liver injury (Lopinavir/ritonavir, remdesivir, chloroquine, complementary alternative medicines) and acute exacerbation in a patient with pre-existing liver disease [25]. The Leukopenia, leukocytosis and lymphopenia have been reported in SARS COV2 infection, with Lymphopenia appears most common > 80% [26-28]. Increase CRP, D Dimer, IL6, LDH and ferritin levels are common. On admission, many patients with pneumonia have normal serum procalcitonin levels; however, in those requiring ICU care, they are more likely to be elevated [11,26,27]. High D-dimer levels and more severe lymphopenia have been associated with mortality [27]. Liver Diseases severity coinciding with a failure of innate immune regulation [28].

These changes can mimic pre existant CLD changes due to bone marrow suppression and cirrhosis associated immune dysfunction syndrome (CAIDS) [29].

COVID-19 in patients with pre-existing liver disease

In a recent meta-analysis by Anand., *et al*. [30]. The presence of CLD does not alter the outcome of COVID-19.The APCOLIS Study (APASL COVID 19 Liver Injury Spectrum Study) [31] showed that metabolism associated fatty liver disease (61%) and viral etiology (60%) were common etiologies. In CLD without cirrhosis, diabetes and in cirrhotics, obesity, predisposed more to liver injury than those without these. 43% of CLD without cirrhosis presented as acute liver injury and 20% cirrhotics presented with either acute-on-chronic liver failure (11.6%) or acute decompensation [(9%)] as per APASL criteria. Child-Turcotte Pugh (CTP) score of 9 or more at presentation, Rising bilirubin and AST/ALT ratio predicted mortality among cirrhosis patients.

Risk of acute-on-chronic liver failure

It is not known whether the patients with chronic liver diseases are more susceptible to develop COVID-19 but these patients are definitely at risk of severe COVID-19 owing to development of acute on chronic liver failure, sepsis and multi-organ failure because of overwhelming inflammatory responses. Thus, protective measures aimed at preventing infection with SARS-CoV-2 and precautions for cirrhotic complications is of utmost importance. These patients have poor immune function and worse outcomes from acute respiratory distress syndrome than the rest of the critically ill population. The incidence of complications in COVID-19 patients and cirrhosis, including hepatic encephalopathy, upper gastrointestinal bleeding and organ failure has not been reported and needs to be assessed in large-cohort clinical studies. There are few case reports on development of ACLF after SARS-COV2 in patients with cirrhosis.

Etiology specific considerations

The data on COVID-19 in patients with liver cirrhosis is limited. The incidence of CLD in patients with COVID-19 in reported series is 0.6 - 37.6%. However, individual data based on type, etiology and severity of CLD is not available.

Patients with alcohol associated liver disease especially severe alcoholic hepatitis are at higher risk of opportunistic infections including SARS-COV2. The timing of initiation of appropriate therapy including corticosteroids is important to improve short-term survival but at the cost of increase risk of severe COVID-19. These patients should be monitored carefully for development of new-onset chest infiltrates, fever and respiratory failure and preferably managed in isolation wards.

Chronic viral hepatitis does not appear to increase the risk of a severe course of COVID19. Patients with chronic hepatitis B not on antiviral therapy are theoretically at risk of reactivation and clinical relapse, if they acquire SARS-COV2 infection. Therefore, antiviral drug compliance in addition to standard precautions are recommended in patients with hepatitis B related cirrhosis. The use telemedicine/local laboratory testing for follow-up visits in patients under antiviral therapy, send follow-up-prescriptions by mail and e-consultations should be preferred. In a recent study, NS5B polymerase inhibitor, sofosbuvir has been shown to have structural homology to remdesivir for the active site of virus and has shown to have in-vitro activity against SARS-COV2, but whether patients with chronic HCV infection on SOF based therapy are protected against SARS-COV2 is unknown.

Patients with NAFLD or steatohepatitis (NASH) usually have diabetes, hypertension and obesity, all of them associated with

a severe course of COVID [32,33]. Further research is needed to understand the impact of COVID-19 in NAFLD. Patients with non-alcoholic fatty liver disease (NAFLD) may suffer from metabolic comorbidities such as diabetes, hypertension and obesity putting them at increased risk of a severe course of COVID-19. Ji and colleagues [22] showed that patients with NAFLD had a higher risk of progression to severe COVID-19 and longer viral shedding time Ji., *et al.* examined 202 patients with confirmed COVID-19, 37.6% of which with non-alcoholic fatty liver disease (NAFLD), and showed that elevated GGT levels portend a more severe course of the disease [22]. In patients with autoimmune liver disease, we currently advise against reducing immunosuppressive therapy. Reductions should only be considered under special circumstances (e.g. medication-induced lymphopenia, or bacterial/fungal superinfection in case of severe COVID-19) after consultation of a specialist. EASL [32], AASLD [35] and Liver transplant society of India [36] have suggested specific guidelines for management of liver patients with COVID 19 infections.

Decompensated cirrhosis and transplant listing

At times of limited hospital beds and health care resources for patients with severe non-COVID diseases, care of patients with decompensated cirrhosis should be maintained according to standard guidelines. Special emphasis to limit exposure such as using telemedicine, phone consultations wherever possible should be done to avoid admission. Listing for transplantation should be restricted to patients with poor short-term prognosis including those with acute-on-chronic liver failure, high model for end stage liver disease (MELD) score and HCC at the upper limits of the Milan criteria, as transplantation activities are likely be reduced. Emphasis on the importance of vaccination for Streptococcus pneumoniae and influenza. Guidelines on prophylaxis of spontaneous bacterial peritonitis and hepatic encephalopathy should be closely followed to prevent decompensation and avoid admission. Include testing for SARS-CoV-2 in patients with acute decompensation or ACLF. Living-donor transplantations should be considered on a case-by-case basis.

Immunosuppressive therapy

Post-transplant management is complex: insufficient immunosuppression results in graft loss due to rejection, whereas excessive immunosuppression may lead to severe infections [37]. Clinical data on COVID-19 infection in liver transplant recipients is still very limited.

Qin., *et al.* described a case of a patient who underwent liver transplantation and experienced COVID-19 infection during the perioperative period Tacrolimus and glucocorticoids were maintained and gradually titrated to lower doses. The patient had no signs of multisystem organ failure during hospitalization and SARS-CoV-2 RT-PCR was negative on discharge. Bin., *et al.* described a case of a 50-year-old male post-liver transplantation who was infected by SARS-CoV-2 [38]. The patient recovered from severe COVID-19 pneumonia after a temporary withdrawal of immunosuppression and administration of a systemic low-dose corticosteroid. On the other hand, Huang and colleagues [39] reported a case of COVID-19 in a patient who had transplantation three years previously for HCC with a poor outcome despite multiple aggressive therapeutic measures. The disease progressed rapidly from mild to critical illness because of multiple nosocomial infections and multiple organ failure. Bhoori., *et al.* [40] described the experience in an Italian transplant center in Lombardy. Three of 111 long-term liver transplant survivors (transplanted more than 10 years ago) have died. Their immunosuppressive regimen had been gradually tapered off, however, all three patients rapidly developed severe respiratory distress syndrome and died in 3 weeks. The authors suggest that post-transplant metabolic complications might outweigh immunosuppression as a risk factor for development of severe COVID-19. Long-term LT recipients seem to be more prone to severe disease than short-term LT patients, suggesting that immunosuppression per se does not increase the risk of severe COVID-19, and that alternatively, the presence of metabolic-related comorbidities typically observed in long-term recipients is responsible for the increased risk of severe COVID-19 in this population.

Liver transplant and COVID 19

Metabolic Comorbidities are the predictors of poor outcome in COVID 19 and this can be applied to the post-transplant metabolic complications (e.g., arterial hypertension, chronic renal insufficiency, diabetes, hyperlipidaemia, and weight gain) might outweigh immunosuppression as a risk factor for development of severe COVID-19 disease in patients who have received liver transplants, in line with data from China, which suggest that comorbidities are associated with a worse prognosis [12,41]. Of these metabolic complications, diabetes might be of particular concern, given its high prevalence (20-40%) in patients undergoing solid organ transplantation [42]. Liver transplantation (LT) decision should be made with caution and at least 28 days after presumptive diagnosis

of COVID-19 [43]. Bronchoalveolar lavage (BAL) should be done for deceased donor liver transplant (DDLT) donor for testing and nasopharyngeal swab for LDLT donor.

Newer drugs and liver disease (Table 1)

So far no therapies demonstrated to be effective in treating or preventing COVID-19, vaccines are still in developmental phase. Following are the important drugs in use for COVID 19 at present [44].

Antiviral therapy (for mild to moderate COVID-19 infection) - Hydroxychloroquine (HCQ), an immunomodulator, increase pH within intracellular vacuoles, commonly used in rheumatological practice, considered safe, has not been associated with liver abnormalities and acute liver injury. Dose adjustments are not necessary in patients with hepatic impairment [45]. Dose is 400 mg PO twice daily for 1 day f/b 200mg PO twice daily for 5 days. Nevertheless, Hydroxychloroquine should be used with caution since there continues to be no high-quality clinical data showing a clear benefit of these agents for COVID-19 and it has the potential to cause harm, including serious cardiac side effects, especially as coadministration with azithromycin [46].

Ivermectin, an anti-parasitic agent, it binds to the Impα/β1 heterodimer thereby preventing Impα/β1 from binding to the viral protein and preventing it from entering the nucleus, this is relatively safe in liver diseases, but can cause self limiting, minor, aminotransferase rise, without significant toxicity, dose is 9 mg single dose [47]. Dose adjustments are not necessary in patients with hepatic impairment [48].

Remdesivir is a nucleotide analogue, with no proved experience in liver cirrhosis. Elevations of transaminase levels have been reported in up to 22.6% of patients [49], it is being used in severe diseases. Dose of Remdesivir is 200mg iv loading followed by 100mg iv for 4 to 10 days. In severe COVID, it can extend up to 10 days. Stop HCQ's before giving this. Dosage adjustment as per eGFR is required, stop if AST/ALT > 5 ULN or if eGFR<30.

Severity of COVID-19	Definition	Non-CLD	Compensated CLD	Decompensated CLD
Mild Symptomatic	Symptomatic (any COVID-19 related symptoms), without pneumonia or hypoxia; and resp rate <24/min	HCQ's/Favipravir/Ivermectin/Sofosbuvir	HCQ's/Favipravir/Sofosbuvir (CTP <9)/Ivermectin	Sofosbuvir (CTP<9)
Moderate	Pneumonia - clinical or radiological, or hypoxia and resp rate ≤30/min, SpO2 ≥90% on room air and no respiratory distress	Remdesivir+ Dexamethasone (6mg)	Remdesivir+ Dexamethasone (6 mg)	Convalescent Plasma Therapy
Severe	Pneumonia and ≥1 of: resp rate >30/min; severe resp distress; or SpO2 <90% on room air	Tocilizumab+Convalescent Plasma Therapy+Remdesivir	Dexamethasone+Convalescent Plasma Therapy+Remdesivir	Convalescent Plasma Therapy
Critical	ARDS or sepsis +/- shock If MELD > 25: Supportive	Remdesivir+ Tocilizumab or Convalescent Plasma Therapy + Dexamethasone if no sepsis	Remdesivir+Convalescent Plasma Therapy+Dexamethasone+/- Tocilizumab	Convalescent Plasma Therapy+ Dexamethasone

Table 1: Proposed treatment for COVID-19 in liver disease.

Favipiravir [50]

Antiviral medication which inhibits the RNA-dependent RNA polymerase. This is available in 200 mg tablet, Dose is 1600 mg in BD on day 1, followed by 600 mg PO BD for 7 - 14 days, but there is no data available in patients with CLD about its use.

Sofosbuvir

Directly acting antiviral (DAA) useful in hepatitis C treatment is a nucleotide analogue and inhibitor of NS5B polymerase. Life cycle of COVID 19 is very similar to HCV, so it can be tried liver diseases, as it considered safe in decompensated liver diseases. Dose is 400 mg once daily PO and it should be avoided if MELD > 25 in CLD [51].

Convalescent plasma therapy

Give as per institutional protocols. Always exclude antibodies before considering CPT, till now mixed results are seen, but only possible logical intervention which can cause neutralisation of viral antigen or its effect [52].

Drugs to combat cytokine storm/systemic hyperinflammation (for severe and critical COVID-19 infection)

Dexamethasone Have been found useful in Cytokine storm and for early recovery, but in liver diseases it can cause immunosuppression and increases risk of infection, should be avoided in decompensated cirrhosis and should be replaced with methylprednisolone in equivalent doses. Dose of dexamethasone used in the Recovery Trial was 6 mg once daily for ten days [53].

Tocilizumab, an interleukin-6 inhibitor, commonly used biological in rheumatological practice, it can results in short lived, asymptomatic, mild elevations of aminotransferase and of bilirubin levels, should be used with cautious in chronic liver diseases, and must be avoided in decompensated liver disease. Dose is 8 mg/kg (maximum 400 mg) iv stat, and to repeat in 24 - 36 hrs if no improvement [54]. Tocilizumab has been used safety and without worsening of disease in patients with concurrent CHC [55]. Importantly, Tocilizumab may increase the risk of HBV reactivation; HBV screening is mandatory and when needed antiviral prophylaxis should follow international guidelines [56].

Future Prospects

Recurrent infections can occur with prolonged stool shedding, even after complete clinical recovery and nasopharngeal swab tested negative and new wave of SARS-CoV-2 infection via a fecal-oral route [17,57]. Methods should be sought for fecal eradication, isolation and stool testing for COVID 19. Thus, in currant scenario, all stool donor for fecal microbiota transplant (FMT) needs to be tested for stool COVID 19 test.

Conclusion

Patients with alcohol associated liver disease especially severe alcoholic hepatitis are at higher risk of opportunistic infections including SARS-COV2. Chronic viral hepatitis does not appear to increase the risk of a severe course of COVID19. Patients with non-alcoholic steatohepatitis and post liver transplant patients usually have metabolic disorders including diabetes, hypertension and obesity, all of them associated with a severe course of COVID. Liver transplantation (LT) decision should be made with caution and at least 28 days after presumptive diagnosis of COVID-19. Post-transplant management is complex: insufficient immunosuppression results in graft loss due to rejection, whereas excessive immunosuppression may lead to severe infections. So far no therapies demonstrated to be effective in treating or preventing COVID-19, vaccines are still in developmental phase, all currant treatment are supportive, not curative.

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