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Review Article

Cytokine Storm of COVID-19 and Its Impact on Patients with and without Chronic Liver Disease

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Abstract

The coronavirus pandemic has resulted in increased rates of hepatic decompensation, morbidity and mortality in patients suffering from existing liver disease, and deranged liver biochemistries in those without liver disease. In patients with cirrhosis with coronavirus disease 2019 (COVID-19), new onset organ failures manifesting as acute-on-chronic liver failure have also been reported. The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) also directly binds to enterocytes and cholangiocytes via the angiotensin converting enzyme receptor 2, although the lung remains the portal of entry. Superadded with the COVID-19 related bystander hepatitis, a systemic inflammatory response is noted due to unregulated macrophage activation syndrome and cytokine storm. However, the exact definition and diagnostic criteria of the 'cytokine storm' in COVID-19 are yet unclear. In addition, inflammatory markers like C-reactive protein, ferritin, D-dimer and procalcitonin are frequently elevated. This in turn leads to disease progression, activation of the coagulation cascade, vascular microthrombi and immune-mediated injury in different organ systems. Deranged liver chemistries are also noted due to the cytokine storm, and synergistic hypoxic or ischemic liver injury, drug-induced liver injury, and use of hepatotoxic antiviral agents all contribute to deranged liver chemistry. Control of an unregulated cytokine storm at an early stage may avert disease morbidity and mortality. Several immunomodulator drugs and repurposed immunosuppressive agents have been used in COVID-19 with varying degrees of success.

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Abbreviations: ACE2, angiotensin converting enzyme 2; ACLF, acute-on chronic liver failure; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; COVID-19, coronavirus disease-19; CRP, C-reactive protein; IL, interleukin; MAPK, mitogen-activated protein kinase; NAFLD, nonalcoholic fatty liver disease; NET, neutrophil extracellular trap; NK, natural killer; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SIRS, systemic inflammatory response syndrome; TNF-α, tumor necrosis factor-alpha.

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Introduction

The novel coronavirus 2019 (COVID-19) disease, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has resulted in a devastating global pandemic, with 113,989,973 confirmed COVID-19 cases, which include 2,531,542 deaths reported by the World Health Organization[1] as of March 2, 2021. COVID-19 has been reported as an air- and surface-borne contagious disease with features of viral pneumonia (fever, cough, lymphopenia, prothrombotic tendency, ground glass opacities on chest radiology) and hypoxemia.[2,3] In addition, alterations in liver chemistries have been reported in patients with and without liver disease, with some reports of increasing severity, complication, and new decompensation, while others refute this possibility. Liver chemistry changes are more likely in those with severe disease and those who have received multiple therapies, requiring high flow oxygen or invasive ventilation.[4] This presents an interesting clinical conundrum, as we need to assess the immunological injury, alteration in liver chemistries and varied clinical course in such patients.[5] We require predictive models of severity of disease, which enable us to prognosticate patients with cirrhosis during the COVID-19 pandemic.[6] In addition, the association between liver chemistries, need for invasive ventilation and COVID-19-associated hospital deaths remains controversial and despite availability of breakthrough vaccines, the pandemic is likely to continue claiming more lives.[7] Given the heterogenous clinical presentation, the spectrum of liver involvement varies from altered liver chemistry in patients without underlying liver disease to progressive decompensation in patients with cirrhosis.[8]

In this review, we have summarized relevant information related to the cytokine storm and pathophysiological basis of liver injury in COVID-19 in those with or without chronic liver disease. The mechanisms of liver injury in COVID-19 are crucial to planning strategies to ameliorate the direct viral, immunological or drug-related liver injury.

Cytokine storm and immune activation in COVID-19

The body's immune system can identify epitopes of the viral antigens of the SARS-CoV-2 via the antigen presenting cells (APCs), like dendritic cells and macrophages, that process the viral antigens and present them to the natural killer (referred to as NK) cells, CD4+ T helper cells and other lymphocytes, which in turn activate CD8+ cytotoxic T cells and B cells. The presentation of viral antigens using the major

histocompatibility complex ensures activation of both the innate and acquired immunity, resulting in proinflammatory cytokines, chemokines, and coagulation enzymes.[9,10] These inflammatory pathways, if dysregulated result in massive activation and 'cytokine storm', a prothrombotic tendency culminating into multiple organ failures and likely death. Pyroptosis is a form of programmed cell death which is an inflammatory caspase-1 dependent type, that occurs in response to infection with intracellular pathogens, such as SARS-CoV-2. Rapid viral replication can result in increased pyroptosis, which can be a precursor for massive release of inflammatory mediators.[10]

In COVID-19, uncontrolled immune response can lead to secondary hemophagocytic lympho-histiocytosis or macrophage activation syndrome, which presents as a life-threatening condition, in the form of persistent fever and pancytopenia quickly progressing into multi-organ failure and increased mortality.[11,12] Macrophage activation syndrome is diagnosed on the basis of clinical and laboratory diagnostic criteria which include fever, increased ferritin, triglyceride levels, pancytopenia, consumptive coagulopathy with hypofibrinogenemia, and splenomegaly.[13,14] Hemophagocytosis is defined as the engulfment of red blood cells, leucocytes, and platelets by macrophages (detected on histology).[13] Besides these features, low or absent NK cell activity and serum CD25 ≥2,400 units/mL is noted.[14] The cytokine storm refers to elevated interferon-alpha, interleukin (IL)-6, IL-1, CCL-5, CXCL8, and CXCL-10. In addition, inflammatory markers like C-reactive protein (CRP) and procalcitonin are frequently elevated.[15,16] Viral features, low interferon levels, increased neutrophil extracellular traps (NETs), and increased pyroptosis lead to impaired SARS-CoV-2 clearance and create the setting for macrophage activation syndrome and cytokine storm. Certain genetic mutations predispose to this condition.[17–19] Once the inflammation sets in, anti-viral treatment will be insufficient to control the disease severity and anti-inflammatory or immunomodulatory drugs are required. Normal antiviral response requires activation of controlled inflammatory syndrome but it is usually overtaken by systemic inflammatory response syndrome (commonly known as SIRS) due to uncontrolled inflammation. Cytokines are the signaling molecules of this response, which are produced by a multitude of immune cells, like dendritic cells, macrophages, neutrophils, NK cells, and adaptive T and B cells.[20] Binding of the COVID-19-associated damage-associated molecular patterns or pathogen-associated molecular patterns to pattern recognition receptors on the immune cells, like lymphocytes and antigen presenting cells, trigger signaling pathways that lead to the cytokine storm.[21,22] Various signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway with Jun NH_2-terminal kinase, extracellular signal-regulated kinase, p65 and p38 MAPK, lead to elution of transcription factors and induce gene expression of several immune regulatory genes encoding proinflammatory cytokines.[23] The MAPK pathways modulate apoptosis and cross-talk between the p38 MAPK pathway and other pathways that can induce cell death.

Other downstream signaling pathways involve JAK1 and 2, Tyk2, and STAT3. Activation of the PI3 kinase/Akt pathway is essential to establish persistent infection with SARS-CoV2.[24]

The major triggered transcription factors are interferon response factors 3 and 7, nuclear factor KB, activation protein 1, and so on.[25] These in turn lead to expression of chemokines, cytokines, and adhesion molecules. The cascade of signaling events leads to recruitment of leucocytes, plasma cells and T cells to the site of infection, where they assist the innate response by macrophages to perform effector function and clear SARS-CoV-2. A counterbalancing mechanism for immune modulation is the negative feedback by the cytokines IL-10 and IL-4, which is often down-regulated in severe COVID-19. This leads to an unregulated and excessive cytokine storm resulting in secondary organ failures (Fig. 1).[26]

COVID-19, cell entry and angiotensin converting enzyme receptor

Although the spread of the SARS-CoV-2 infection is by droplet infection and the primary entrance is the respiratory tract, it also infects the gastrointestinal tract directly. The angiotensin converting enzyme 2 (ACE2) receptor is present on type II alveolar cells in the lung, esophageal epithelium, enterocytes of the ileum and colon, pancreas, hepatocytes and cholangiocytes, myocardium, proximal tubular cells of the nephron, and the pancreas.[27,28] The resultant inflammatory response may lead to viral clearance but when uncontrolled (in the form of cytokine storm), it can lead to vascular barrier damage, alveolar membrane integrity damage, multiorgan failure, and ultimately death.[29,30] Although the primary site affected is the lung, with acute lung injury and acute respiratory distress syndrome (ARDS), the liver is also affected by a similar mechanism (Fig. 1).

The ACE2 receptor is highly expressed on well-differentiated enterocytes, and this explains why fecal shedding of the virus is detected and diarrhea is a symptom of COVID-19. Gastrointestinal manifestations are noted in up to 61% of COVID patients. ACE2 receptors are present at various gastrointestinal sites, like gastric and duodenal glands and distal enterocytes. COVID-19 can present as malabsorption, altered intestinal permeability, and activation of the enteric nervous system. SARS-CoV-2 is a systemic infection and the intracellular vesicles containing the virus remain *in situ* for long after apparent recovery from the disease. Pathological examination of patients with liver disease shows the liver histology has microvesicular steatosis, as well as areas of focal necrosis with lymphocyte infiltration like reports of bystander hepatitis caused by immunological injury attributable to influenza virus. SARS-CoV-2 could also cause direct cytopathic injury to the liver, other than hypoxic, or free radical-mediated injury. The virus has also been detected in up to 41% of autopsied livers with a viral load of 1.6×10^6 copies per gram of liver tissue.[31,32] Down-regulation of the negative feedback counterregulatory IL-10 and IL-4 mechanism results in a hyperinflammatory cytokine storm.[9]

ACE2 expression in cell clusters is higher in cholangiocytes than in hepatocytes (59.7% vs. 2.6%), but immune-mediated hepatitis is more likely to be the explanation for deranged liver chemistries, as with other respiratory tract viruses.[33,34] With such a broad infection footprint, many drugs affecting the immune cascade have been tried. Use of the anti-IL-6 agent tocilizumab, hydroxychloroquine and steroids are examples, which have shown a varied efficacy.

Viral kinetics of SARS-CoV2 in cirrhosis

Cirrhosis is an immunocompromised state, and it appears there is impaired viral clearance of the SARS-CoV-2. The virus resides in double membrane vesicles, which prevent creation of pattern recognition receptors, and even after the PCR test being negative, the lung alveolar cells and macrophages can show tell-tale signs of these viral vesicles, even after 2 weeks of apparent resolution of disease.[2,21]

In cirrhosis, there is also a lower level of type I interferon, which results in impaired viral response. Neutrophils also contribute to viral clearance by release of free radicals, degranulation of vesicles, and secretion of antimicrobials through the formation of unique NETs.[35] Neutrophils are activated by IL-8, CXCL8, leukotriene B4 or lipopolysaccha-

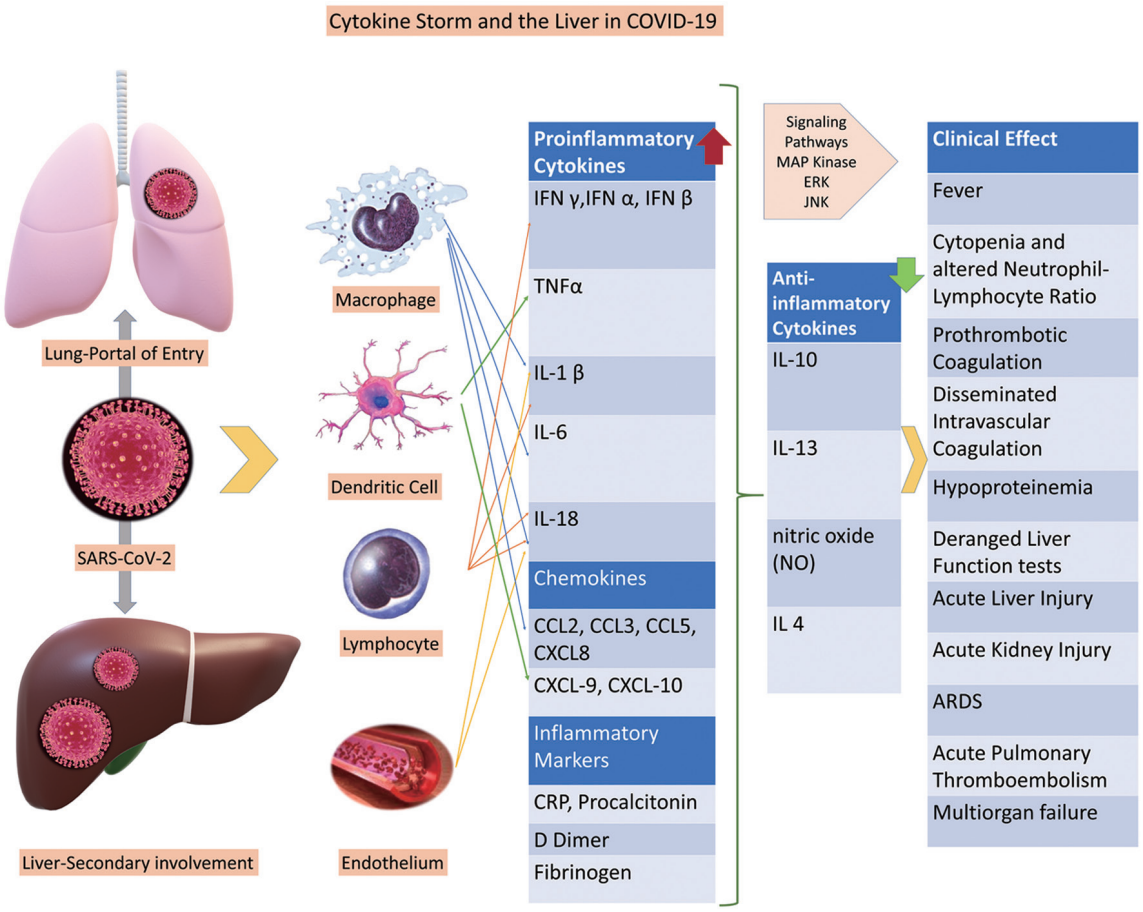

Fig. 1. COVID-19, cytokine storm and immune-mediated organ failure.

ride, and generate a programmed cell death with a chromatin reticular framework covered with neutrophil granule-derived peptides and proteolytic enzymes. This generates a net-like structure, in which pathogens get trapped, aptly called NETs. The positively charged histones of the chromatin network of NETs can bind to and immobilize negatively charged viral envelope of the SARS-CoV-2 particles.[36,37]

COVID-19 and hepatic involvement in people without liver disease

COVID-19 results in liver injury, transaminitis and even impending liver failure in patients without liver disease, especially those with moderate to severe illness. Hypoxemia, impaired cardiac function, and reduced tissue perfusion in severely ill COVID-19 patients can lead to increased vulnerability of an apparently healthy liver. The mechanisms of liver injury in a native 'healthy' liver are multifactorial. Direct viral cytopathic effects, hypoxic injury, hepatotoxicity from therapeutic drugs, and secondary damage due to multiple organ dysfunction are the most likely underlying mechanisms for liver injury. On histopathology, a mild increase in sinusoidal lymphocytic infiltration, sinusoidal dilatation, mild steatosis, and multifocal hepatic necrosis are noted. Direct cytopathic effects of the SARS-CoV-2 are multiple foci of necrosis in the periportal area (zone 1) and adjacent to terminal hepatic veins (zone 3), with minimum inflammation. The described histology is like non-viral related acute liver injury. Conspicuous absence of dense inflammation, widespread necrosis, ballooning, Mallory hyaline, or pericellular fibrosis, cholestasis or lack immune mediated damage differentiates it from viral hepatitis.[38,39]

Biochemically, abnormal liver chemistries in COVID-19 include elevation of aspartate transaminase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase, but bilirubin and alkaline phosphatase changes are seen rarely. In absence of liver disease, liver failure is rare. A recent meta-analysis[5] showed that the liver chemistries per se did not affect outcomes in patients with mild and moderate COVID-19 infection.

Table 1 shows the list of studies which provided data on liver injury in patients without underlying liver disease.[40–42]

COVID-19, inflammation, coagulation, and liver disease

The cytokine storm triggered by COVID-19 has several implications in those with liver disease. Firstly, patients with cirrhosis are already in a procoagulant rebalanced state and are predisposed to pulmonary microthrombosis.[43] The systemic inflammatory state is difficult to diagnose, as patients frequently have an elevated CRP and a preexisting cytopenia and splenomegaly attributable to portal hypertension. Due to the hyperdynamic circulation, patients with decompensated cirrhosis already have endothelial inflammation, elevated baseline norepinephrine, and are at increased risk

Table 1. List of studies which provided data on liver injury in patients without underlying liver disease

No.	Reference	Study type	No. of patients with COVID-19	Pre-existing liver diseases	Hepatobiliary function markers	Inflammatory markers and other relevant blood tests	Proposed possible theories of hepatic injury
1	Xie H[40]	Retrospective case series	79	Patients with previous liver diseases were excluded	31.6%, 35.4% and 5.1% of patients had elevated ALT, AST and TBIL, respectively. Median (range) values were 36.5 (17.5–71.5) U/L, 34.5 (25.3–55.3) U/L and 12.7 (8.1–15.4) mmol/L, respectively	CRP (max.,79.6 μmol/L) and ESR (max., 58 mm/h) increased; while LYM reduced (min., 0.9×10^9/L)	Overall disease exacerbation; disease severity. Males were more likely to have liver injury when infected with COVID-19 ($p<0.05$); compared with patients without liver injury, patients with liver injury had increased levels of white blood cell counts, neutrophils, CRP and CT score ($p<0.05$) and had a longer length of stay ($p<0.05$)
2	Zhang Y[41]	Retrospective case series	115	Two patients had chronic hepatitis B (excluded)	ALT and AST increased in 9.57% and 14.78% patients, respectively on admission. TBIL elevation was rarely observed. Mean levels higher in severe cases	54.78% had reduced ALB, significantly lower in severe cases. 57.39% had increased CRP, higher in severe cases (80.75+69.18). LDH level (mean+SD:346.10+ 257.26) significantly elevated in severe cases	Dysfunction of immune system. Levels of ALT, AST, TBIL, LDH and INR showed statistically significant elevation in severe COVID-19 cases compared with that in mild cases
3	Huang C[3]	Prospective case series	41	Chronic liver disease in one patient	AST (max., 48.0 U/L) increased in 37%, more in the ICU group	73% had LDH >245 U/L (max., 408 U/L). 37% had LYM $>1.0\times10^9$/L (max., 1.1×10^9/L)	Overall disease exacerbation: cytokine storm. Compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, MCP1, MIP1A, and TNF-α
4	Fan Z[42]	Retrospective case series	148	None described	55 patients (37.2%) had abnormal liver function at hospital admission. Elevated ALT (n=27; 41–115 U/L), AST (n=32; 37–107 U/L), γ-glutamyl transferase (n=26; 48–159 U/L), ALP (n=6; 102–144 U/L), and total bilirubin (n=9; 21–46.6 μmol/L)	PCT and CRP elevated in those with abnormal liver function	More patients with abnormal liver function (57.8%) received treatment with lopinavir/ ritonavir compared with those with normal liver function (31.3%; p=0.01)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C Reactive protein; G-CSF, granulocyte colony stimulating factor; ICU, intensive care unit; LDH, lactate dehydrogenase; LYM, lymphocyte; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; PCT, procalcitonin; SD, standard deviation; TBIL, total bilirubin.

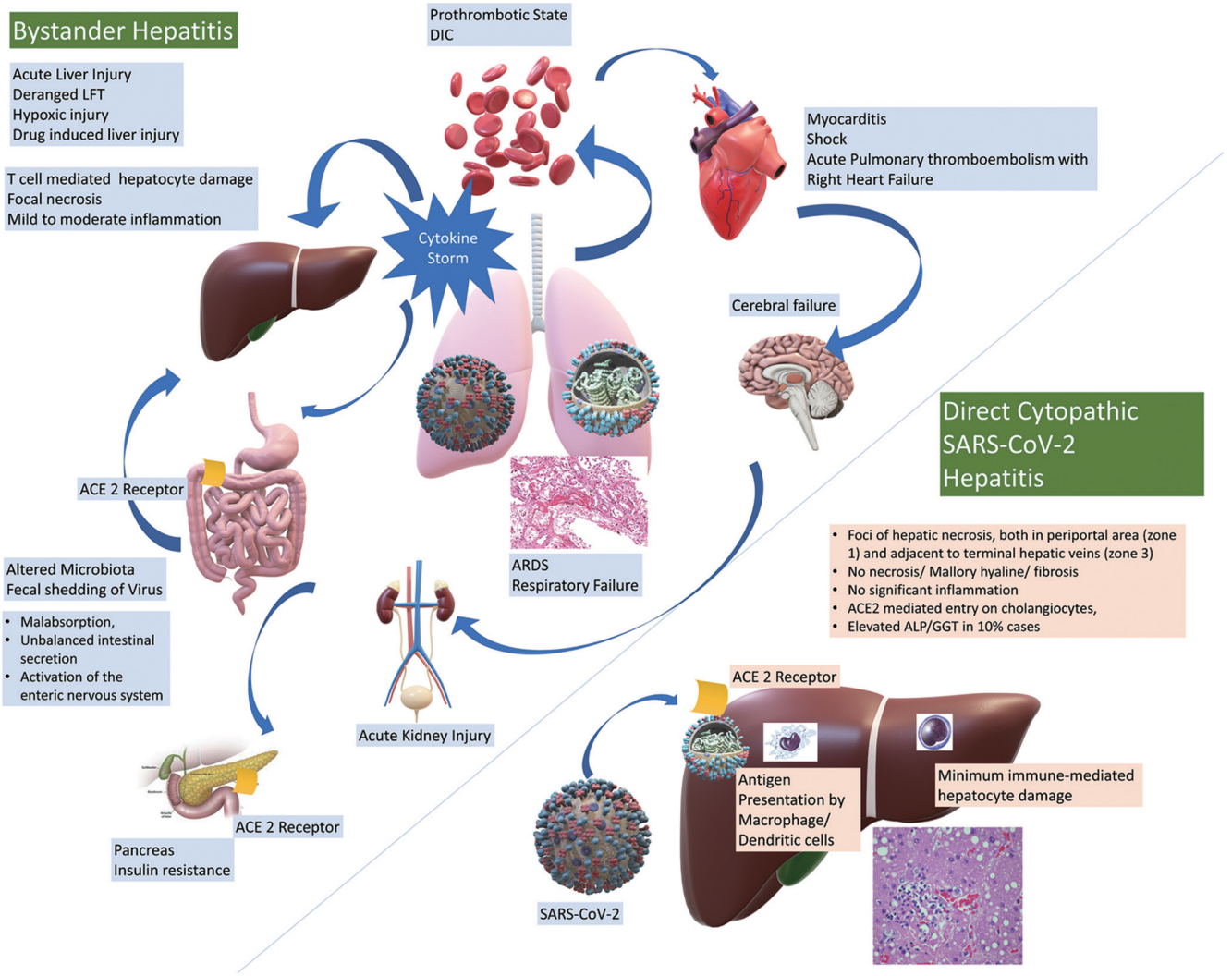

Fig. 2. Etiopathogenesis of liver injury in COVID-19.

of thromboembolism and ARDS.[44,45] The procoagulant tendency of COVID-19 is due to systemic endothelial activation, or damage mediated by viral binding to the ACE2 receptor on the endothelium and other organs. In addition, presence of comorbidities, mechanical ventilation, and bedridden state favor venous thromboembolism.[42]

The resultant influx of inflammatory mediators raises blood viscosity, and in presence of venous catheters or dialysis access, there is possibility of deep vein thromboses in cirrhosis and liver failure. Patients with predisposing risk factors like coronary artery disease and stroke are also affected by the cytokine storm and have increased risk for cardiac or cerebrovascular events when they have metabolic liver disease. Patients with liver disease often fare poorly in an intensive care setting during for viral pneumonia with respiratory failure, like COVID-19 and H1N1 influenza infections.[42,46–48] Although patients with cirrhosis are likely to benefit from prophylactic anticoagulation with low molecular weight heparin, they are also at increased risk of variceal bleeding due to increased portal pressure triggered by new onset bystander hepatitis. (Fig. 2). Also, endogenous heparinoids are produced in patients with liver failure with cytokine storm or cirrhosis with systemic inflammation, which affect coagulation and predispose to bleeding. Therefore, using balancing anticoagulants in patients with cirrhosis with COVID-19 with a cytokine storm harbors inherent bleeding risk on one hand and pulmonary microthrombosis on the other.[49] The terminal events in these patients with cirrhosis with COVID-19 have been progressive respiratory failure, with secondary organ failures like cardiac or renal failure requiring inotropic support, secondary sepsis, variceal bleeding, or sometimes sudden cardiac events.[50,51] In the multicentric APCOLIS study[52] of 288 patients, 43% of patients with liver disease presented as acute liver injury, 20% presented as acute-on-chronic liver failure (commonly referred to as ACLF) or acute decompensation (9%). A Child Turcotte Pugh score >9 predicted mortality with hazard ratio of 19.2 (95% confidence interval: 2.3–163.3), with sensitivity of 85.7% and specificity of 94.4%. Patients with liver disease have poor outcomes in the setting of invasive ventilation. Improved intensive care, timely interventions and monitoring altered liver chemistries can improve outcomes.[53]

Other associations, such as presence of chronic hepatitis B, did not increase the mortality risk. Therefore, it appears that the cytokine storm is one of the important defining fac-

tors contributing to morbidity and mortality in those with liver disease.[54] A raised AST and direct bilirubin at baseline were independent predictors of COVID-19 mortality.

When acute liver injury and ACLF were reported in patients with liver disease, it was typically seen in the setting of multiple organ failures, severe pneumonia or ARDS. After propensity matching, the baseline and peak values of liver function tests, the trajectory of COVID-19 and severity of liver scores and outcomes are often equivalent in those with compensated cirrhosis.[54,55] In contrast, in decompensated liver disease, there is a marked risk of COVID-19-associated liver and coagulation failure. Particularly, studies have reported such events in patients with Child-Turcotte-Pugh B and C cirrhosis with increased decompensation events like ascites, coagulopathy, and hepatic encephalopathy and in-hospital mortality. In view of the increased morbidity and mortality, it is essential to protect patients with decompensated cirrhosis and provide guidance to better manage and evaluate patients with COVID-19 and its complications.[56]

Table 2 shows the list of studies which included patients with underlying liver disease, and significant findings.[57–63]

COVID-19, obesity and fatty liver disease

A recent paper by Bramante *et al*.[64] showed that presence of nonalcoholic fatty liver disease (NAFLD) is associated with increased risk of hospital admission [odds ratio: 2.04 (1.55, 2.96, $p<0.01$)]. In another study[65] on 202 NAFLD patients with COVID-19, altered liver chemistries were noted in 75% during hospital stay. About a third of patients with NAFLD continued to have raised transaminases even on follow up, suggesting a long-lasting superadded insult to the fatty liver. Male sex, age >60 years, high body mass index, presence of comorbidities and NAFLD were associated with progression to severe COVID-19 disease. On logistic regression, NAFLD was an independent risk factor for COVID-19 progression, high likelihood of ongoing liver injury and raised liver chemistries during hospital stay, and prolonged duration of viral shedding. It appears that presence of obesity, NAFLD and metabolic syndrome are associated with an increased risk of COVID-19 progression.[66]

Drugs targeting the cytokine storm

Several drugs have been tested in COVID-19 based on the assumption that dysregulated immune responses need to be curbed. One of the main therapies includes the use of steroids, either prednisolone or methylprednisolone or intravenous hydrocortisone, which act through the glucocorticoid receptor and effector genes. As per the World Health Organization guidelines, systemic corticosteroid therapy is not for routine use. It should only be given to those with cytokine storm, ARDS, acute heart failure, acute kidney injury, and high serum levels of D-dimer.[67] Anti-rheumatic drugs, hydroxychloroquine, chloroquine, JAK inhibitors, IL-1 and IL-6 inhibitors, anti-tumor necrosis factor-alpha (commonly referred to as TNF-α) drugs, corticosteroids, colchicine, and intravenous immunoglobulin. The use of chloroquine and hydroxychloroquine was reported to reduce COVID-19-mediated injury, by arresting the cytokine storm or the activation of CD8+ cells, or by preventing endocytosis-mediated uptake of the virus. Chloroquine and hydroxychloroquine act by accumulating in lysosomes, increasing the pH of the endosome, thereby interfering with viral entry or exit from the cells. Also, these drugs interfere with the ACE2 receptor, preventing entry of the SARS-CoV-2. Chloroquine and hydroxychloroquine may reduce glycosylation of the ACE2 receptor which prevents the virus binding to and entering the new cells. However, major trials have found no putative benefit for prophylaxis of COVID-19, and gradually these drugs have been disregarded.[68] Similarly, other direct antivirals like remdesivir and favipiravir also failed to show significant efficacy or survival benefit.[69,70] Tocilizumab, a humanized IgG1 monoclonal antibody to the IL-6 receptor, has been used with limited success in COVID-19. The recommended dose of tocilizumab is 8 mg/kg intravenous as single or two divided doses at 12 to 24 h intervals, with a maximum dose of 800 mg. However, the adverse events include increased propensity of infection, hypertriglyceridemia, diverticulitis, and hepatotoxicity.[71]

Several repurposed drugs have been adopted from rheumatology practice to assess amelioration of the cytokine storm in COVID-19. Colchicine has been recommended as potential therapy for complications of COVID-19, as an IL-1 inhibitor.[72] Other drugs include a recombinant humanized anti-IL6 receptor antibody called sarilumab, a recombinant human mouse chimeric monoclonal antibody called siltuximab, and an IL-1 blocker called anakinra.[73,74] Anakinra, an anti-rheumatic drug, was studied in the trial setting to inhibit pathological effects of IL-1 alpha and IL-1 beta.[75] Other than drugs that directly inhibit the immune response, cytokine dialysis has also been tried, using blood ultrafiltration, diffusion, and adsorption circuits in dialysis machines. Restoration of the immune IL-6/IL-1 levels and other proinflammatory molecules theoretically protects against organ failures but clinical efficacy is still unclear, and the immune dysregulation is only one problem of many. A novel treatment approach for preventing and managing the cytokine storm using mesenchymal stem cell-based immunomodulators has been proposed. Intravenous transplantation of mesenchymal stem cells was shown to be effective in COVID-19 in a trial.[76]

Relevance of the cytokine storm in COVID-19

After describing the various aspects of the cytokine storm, it is important to emphasize that the condition has no definition. In most studies on COVID-19, it is described as a hyperimmune response characterized by the release of ILs, interferon, TNF, chemokines, and other mediators. These represent a normal response to a variety of pathogens, and the term 'cytokine storm' implies that these released cytokines are injurious to the host; furthermore, there is no consensus yet as to the levels of permissible cytokines that distinguish a well-conserved innate immune response from a dysregulated hyperinflammatory immune response. In addition, all the signaling pathways described have regulatory and counterregulatory responses and pleiotropic downstream mediators that may be acting in complex dependent activities that cannot be easily predicted. To complicate matters, it is unclear if the cytokine storm is pathogenic or protective in an individual patient.[77] The abject failure of some drugs like tocilizumab, anakinra, etc. is a case in point and should dampen the enthusiasm displayed globally for applying drugs for one condition without much success in another. It is time to reinterpret and define the cytokine storm. The role of T cells that exert protective functions by reigning in on overactive innate immunity is important, as lymphopenia is associated with ARDS.[78] The important role of microthrombosis in the pathogenesis of severe pneumonia and outcomes related to hypoxemia with secondary organ failures is often under-played. The failure of the use of immunomodulators used in rheumatological conditions should make us reassess the degree of cytokine storm and possibly use therapy in patients with demonstrated high levels of cytokines. The cytokine release syndrome was described by Maude *et al*.[79] in recipients of chimeric an-

Table 2. List of studies which included patients with underlying liver disease, and significant findings[61–67]

No.	Reference	Study type	No. of patients with COVID-19	Pre-existing liver diseases	Hepatobiliary function markers	Inflammatory markers and other relevant blood tests	Proposed possible theories of hepatic injury
1	Wang D[57]	Retrospective case series	138	Chronic liver disease in 2.9% of patients	No significant liver abnormalities	LYM (median: 0.8×10^9/L) reduced in 70.3% of cases, and LDH (median: 261 U/L) increased in 39.9% of patients	Overall disease exacerbation
2	Cai Q[58]	Retrospective case series	298	2.7% had liver disease. CHB (1.7%). NAFLD (4.7%). ALD (3%)	14.8% experienced liver injury, with ALT max., 59.5 U/L and AST max., 65 U/L: 8.7%, respectively	CRP (max., 47.13 mg/dL) increased in 70% cases	Overall disease exacerbation. Liver injury mainly occurred in severe patients (36.2% vs. 9.6%, $p<0.001$)
3	Xu XW[59]	Retrospective case series	62	12% had underlying liver disease	AST (max., 32 U/L) increased in 16% of patients	42% showed LYM reduction	None described
4	Shi H[60]	Retrospective case series	81	Hepatitis or liver cirrhosis in 9% of cases	AST (>40 U/L) increased in 53% of patients, lower in asymptomatic patients	CT imaging described	None described
5	Zhang B[61]	Retrospective case series with the data of non-survivors	82	Liver diseases in 2.4% cases. Patients who died had comorbidities (76.8%), including hypertension (56.1%), heart disease (20.7%), diabetes (18.3%), cerebrovascular disease (12.2%), and cancer (7.3%)	ALT (>40 U/L), AST (>40 U/L), and TBIL (> 20.5 mmol/L)	LYM ($<1.0\times10^9$/L), ALB (<40 g/L) and CD8+ cells ($<220\times10^9$/L). CRP (100%), lactate dehydrogenase (93.2%), and D-dimer (97.1%). IL-6 >10 pg/mL used as cut-off	–
6	Guan WJ[62]	Retrospective case series	1,099	Hepatitis B in 2.1% of patients	AST >40 IU/L (22.2%). ALT >40 IU/L (21.3%)	PCT >0.5 ng/mL (5.5%)	–
7	Li L[63]	Retrospective case series	85	Hepatitis B, alcoholic liver disease, and fatty liver disease ($n=2$ in each category)	24.7% had ALT elevation at admission	CRP ≥20 mg/L and LYM count $<1.1\times10^9$/L were independent risk factors for hepatic injury. ALB (mean: 33.4 g/L) in the ALT-elevated group was significantly lower	Inflammatory cytokine storm. Deterioration of the disease with a dynamic process. Limitation: 6 in the elevated-ALT group ($n=33$) had a history of liver disease (i.e. HBV infection, alcoholic liver disease, fatty liver)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C Reactive protein; HBV, hepatitis B virus; LDH, lactate dehydrogenase; LYM, lymphocyte; NAFLD, nonalcoholic fatty liver disease; PCT, procalcitonin; TBIL, total bilirubin.

tigen receptor T cell therapy, where the peak plasma IL-6 level was approximately 10,000 pg/mL, which was almost 1,000-times higher than the level reported in severe COVID-19. Hence, a consensus definition and diagnostic criteria for the cytokine storm is the need of the day.[80]

Summary

The COVID-19 crisis has presented an enormous challenge to the medical community, as it is a multisystem disease with high mortality and secondary attack rate in predisposed individuals, requiring a multidisciplinary approach for diagnosis, prognostication, and management decision plans. Several therapeutic agents have been tried to manage the hyperinflammatory cytokine storm which leads to immune-mediated organ damage. The trial and failure of several agents like hydroxychloroquine, remdesivir, chloroquine, etc. underlines the fact the evidence-based practice is still unable to provide an answer for controlling the cytokine storm. Strategic vaccination is now a reality, but the story of COVID-19 suggests that we need to be prepared to provide treatments which can manage and control the deleterious effects of our immune reaction, while retaining the viral clearance and disease-controlling immune mechanisms.

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Conflict of interest

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Author contributions

Conceptualization and original draft preparation (MP), conceptualization, reviewing and editing of the manuscript (CKK). Both authors approved the final version of the manuscript.

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