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Insight into the liver dysfunction in COVID-19 patients: Molecular mechanisms and possible therapeutic strategies

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Abstract

As of June 2022, more than 530 million people worldwide have become ill with coronavirus disease 2019 (COVID-19). Although COVID-19 is most commonly associated with respiratory distress (severe acute respiratory syndrome), meta-analysis have indicated that liver dysfunction also occurs in patients with severe symptoms. Current studies revealed distinctive patterning in the receptors on the hepatic cells that helps in viral invasion through the expression of angiotensin-converting enzyme receptors. It has also been reported that in some patients with COVID-19, therapeutic strategies, including repurposed drugs (mitifovir, lopinavir/ritonavir, tocilizumab, etc.) triggered liver injury and cholestatic toxicity. Several proven indicators support cytokine storm-induced hepatic damage. Because there are 1.5 billion patients with chronic liver disease worldwide, it becomes imperative to critically evaluate the molecular mechanisms concerning hepatotropism of COVID-19 and identify new potential therapeutics. This review also designated a comprehensive outlook of comorbidities and the

impact of lifestyle and genetics in managing patients with COVID-19.

Key Words: COVID-19; Liver damage; Pharmacotherapy; Cytokine storm; Molecular mechanisms

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Core Tip: Several review articles have contributed to the pathophysiology, therapeutic strategies, vaccine development, and clinical trials of coronavirus disease 2019 (COVID-19). Since the liver is the primary site of immune protein synthesis, any liver defect may compromise the immune system. Patients with chronic liver disease are at a higher risk of severe COVID-19. This review article demonstrated the pathophysiology and molecular mechanisms responsible for more severe outcomes in patients with hepatic defects. Further, we critically evaluated the molecular mechanisms concerning hepatotropism in patients with COVID-19, which could lead to the development of new therapeutics.

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INTRODUCTION

On December 31, 2019, reports surfaced of patients with an unusual severe acute respiratory syndrome (pneumonia) in Wuhan, China. On January 7, 2020, the causal agent responsible for the mysterious deaths was branded as coronavirus disease 2019 (COVID-19) by the International Classification Committee of Viruses[1]. A severe global pandemic was declared on March 11, 2020. Since then, there have been 623893894 confirmed cases of COVID-19, including 6553936 deaths as of October 21, 2022[2].

The clinical manifestation of COVID-19 is usually interpreted as severe lung infection (acute respiratory distress syndrome), causing turmoil in the patient's respiratory system and even death[3]. Many individuals admitted to intensive care units were known to have hepatic and heart-related complications[4]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with chronic liver disease leads to an elevated and dysregulated immune response[5]. Even healthy individuals infected with COVID-19 displayed liver dysfunction, increasing morbidity and mortality of such patients[6].

Hepatologists have been working to deduce the relationship between COVID-19 and the liver. About 300 million patients with chronic liver diseases in China alone had severe COVID-19 symptoms[7]. It was advocated that SARS-CoV-2 invasion might trigger reactivation of existing liver disorders in the patient, causing hepatotoxicity[8]. In addition, hepatic patients are more prone to COVID-19 infection[9]. Some COVID-19 cases have reported multiorgan failure significantly increasing cytokine levels, including vascular endothelial growth factor, interleukin (IL)-6, macrophage inflammatory protein 1 α , and macrophage inflammatory protein 1 β [9-11].

Since the liver is a primary site of the synthesis of proteins associated with immunity, it inhibits infectious microbes from entering the bloodstream from the gut. Any liver defect would thus cause a compromised immune system[12]. Increased levels of hepatic biomarkers including alanine transaminase and aspartate transaminase indicate a close pathophysiological association between the liver and COVID-19. Obesity predisposes individuals to metabolic disorders, diabetes, and insulin resistance, which can lead to chronic liver disease and may culminate into cirrhosis, fibrosis, and even hepatocellular carcinoma[13]. This indicates a dire need to investigate the pathophysiology and molecular mechanisms responsible for hindering the immune system, which leads to more severe outcomes in patients with cardiovascular and hepatic defects[14]. In this article, we comprehensively evaluated the invasion and spread of SARS-CoV-2 as a tool to improve therapeutic strategies against liver damage in patients with COVID-19.

ORIGIN OF SARS-COV-2: A BOTTOM-FEEDER OPPORTUNIST

The beta coronavirus isolated from COVID-19 patients was identified using whole genome sequencing and matrix representation with parsimony phylogenetic analysis[15,16]. This virus is the closest relative of *Rhinolophus affinis* virus (bat CoV RaTG13) with more than 96% similarity[17,18]. Thus, the bat is

Table 1 Summary of severe acute respiratory syndrome coronavirus 2 strains and mutations that enhance viral entry into the host cell

Sr. No.	Strain	Mutation	Host entry	Location	Time of first report	Ref.
1	Alpha (B.1.1.7)	N501Y mutation on the RBD	The affinity between RBD and ACE2 is significantly increased	United Kingdom	December 2020	[40-42]
2	Beta (B.1.351)	N501Y mutation on the RBD N417/K848/Y501	The affinity between RBD and ACE2 is significantly increased	South Africa	December 2020	[41-43]
3	Gamma (P.1)	N501Y mutation on the RBD N417/K848/Y501	The affinity between RBD and ACE2 is significantly increased	Brazil	January 2021	[41,42,44]
4	Delta (B.1.617.2)	Absence of N501Y mutation	No effect	India	December 2020	[41,42]
5	Omicron (B.1.1.529)	N501Y mutation on the RBD	The affinity between RBD and ACE2 is significantly increased	South Africa	November 2021	[41,42]

RBD: Receptor binding domain; ACE2: Angiotensin-converting enzyme 2.

hypothesized to be its most suitable natural host. The phylogenetic interrelationship is depicted in Figure 1. Whole genome studies revealed the presence of three SARS-CoV-2 strains (A, B, and C) among various human populations[19]. Originally strain A was found in the European population and was regarded as the ancestral strain closest to the bat coronavirus[20,21]. Strain B was primarily found in East Asian populations[22]. Strain C, however, was more common among Americans, thus defining and tracking their outbreak areas[23]. Although the phylogenetic relationship of SARS-CoV-2 is still under investigation, it is well established that the preferred reservoir host of this virus is the bat and was transferred to humans from consumption of wild bats[18,24,25]. These are undoubtedly among the most prevalent RNA viruses (positive sense) that can infect a wide range of hosts[6,26]. Whole genome sequencing demonstrated that SARS-CoV-2 is most closely related to the CoV RaTG13 virus[27,28].

After almost three years since the discovery of SARS-CoV-2, the mechanism that allows SARS-CoV-2 to jump to a human host and invade hepatocytes remains unclear. Upregulated transaminases in patients with COVID-19 indicate a strong link between SARS-CoV-2 and liver injury[29,30]. The genetic algorithm for detecting recombination demonstrated that SARS-CoV-2 possesses a mosaic genome comparable to five coronaviruses (probable donor strains), namely *Rhinolophus affinis* RaTG13 coronavirus, *Rhinolophus pusillus* RpYN06, *Rhinolophus pusillus* BANAL-103, *Rhinolophus malayanus* RmYN02, and *Rhinolophus malayanus* BANAL-52[31-33]. The spike protein of SARS-CoV-2 has more similarity with *Rhinolophus affinis* RaTG13, and human angiotensin-converting enzyme 2 (ACE2) interaction is closely related to *Rhinolophus malayanus* BANAL-52. Another noteworthy feature is the absence of furin cleavage sites in all of these viruses[34].

SARS-CoV-2 has a deadly combination of disease severity and transmissibility[35,36]. Coronaviruses are remarkable entities (125 nm in size) with one of the heaviest viral RNA genomes, accounting for 30000 nucleotides and equipped with an extraordinary ability to correctly repair drug-induced mutations[37]. The chances of zoonotic transmission or accidental spill-over through exponential proliferation are also possible. In addition, a new host like a human would lack previous immunity to the pathogen, which provides a compatible incapacitating host defense mechanism[38]. Above all, the increasing human-animal interactions due to deforestation, hunting, domestication, wet market, and wild animals as a food source in many countries further increases the chance of viruses to adapt to infect humans[39]. Five SARS-CoV-2 strains are currently prevalent[40-44] (Table 1).

Prognosis and pathophysiology: thwarting effects of SARS-CoV-2 on patients with existing liver diseases

Various factors govern the prognosis of this disease based upon pre-existing health conditions, comorbidity, age, course of treatment adopted, and the response to treatment. The overall fatality rate is above 2%. Like most pathogens, the liver serves as one of the preferred sites of proliferation spots for coronaviruses because it is a common gateway for the blood[45,46]. It has been observed in many studies that one-third of patients with COVID-19 develop liver dysfunction, which was more frequent among elderly, male patients[47]. A survey conducted on 4000 seriously ill COVID-19 patients confirmed an inflated mortality rate after 3 mo, causing death in 31% of the patients[48]. Autopsies and post-mortem biopsies of the liver revealed infection of cholangiocytes, hepatocytes, and endothelial cells with SARS-CoV-2, which led to severe liver damage. Mechanisms of injury include major hepatocyte ballooning, eosinophilic action creating a cytokine storm, hypoxia, and ischemia leading to liver necrosis (Figure 2)[49-51].

Hepatic fat accumulation indicating microvesicular steatosis is a clear consequence of SARS-CoV-2 [52]. Additionally, lobular inflammation and fibrosis cause severe liver cirrhosis. Cirrhosis further reduces blood flow through the liver, thereby increasing blood pressure in the hepatic vein, which is

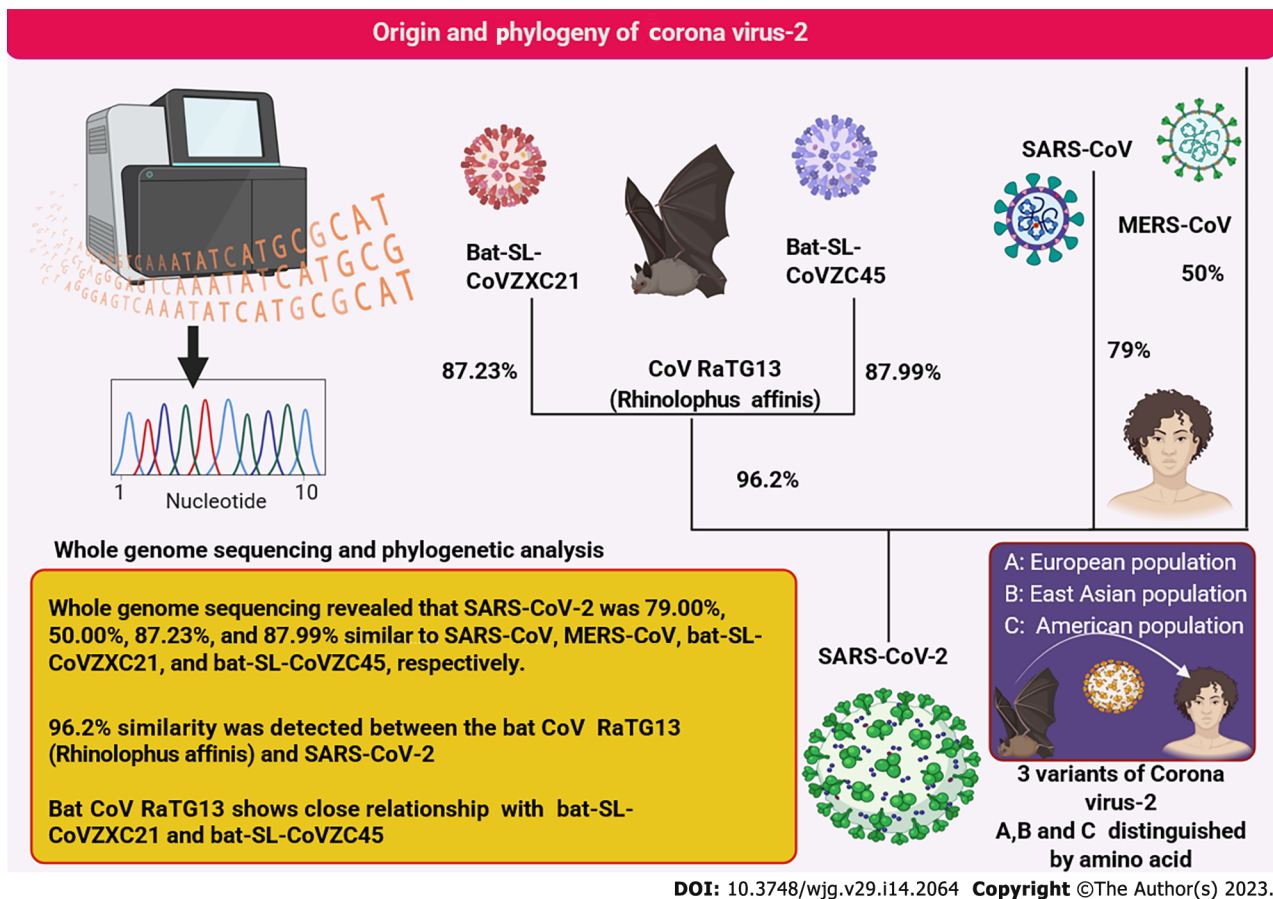


Figure 1 The origin and ancestral relationship of severe acute respiratory syndrome coronavirus 2 with other related viruses. Whole genome sequencing revealed that severe acute respiratory syndrome coronavirus 2 virus was most closely related to the CoV RaTG13 virus. The variant strains of coronavirus and their biogeographical distribution are illustrated. MERS-CoV: Middle East respiratory syndrome coronavirus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; R. affinis RaTG13: SARS-like coronaviruses: Bat-SLCoVZX.

supplied by the intestines and spleen. Once SARS-CoV-2 enters the human body, major histocompatibility complexes ensure the release of proinflammatory (acquired and innate)[53-55]. SARS-CoV-2 binds to the ACE2 receptor to enter the target cells[56]. These receptors are typically expressed on the bile duct epithelial cells, sinusoidal and capillary endothelial cells, and hepatocytes[57-59]. The viral antigen epitopes are recognized by antigen-presenting cells (macrophages and dendritic cells). They are presented to CD4+ T helper cells, lymphocytes, and natural killer cells, which activate B cells and CD8+ cytotoxic T cells[60-63].

Several patients with COVID-19 have abnormal biochemistry, displaying fluctuating levels of vital enzymes and biomolecules concerning hepatobiliary manifestations[64]. Patients with COVID-19 have decreased hepatic functions, typically displayed as increased liver enzymes and alanine transaminase and aspartate transaminase levels[5,65-67]. Several case studies observed these findings in more than 50% of critically ill COVID-19 patients[68]. Liver injury, chronic congestion, and nodular proliferation in patients with COVID-19 may occur, with more than 70% of patients developing steatosis[69,70]. The pathogenesis of hepatic damage in patients with COVID-19 is multifactorial, including pre-existing hepatic disease, hypoxia, ACE2 aided viral invasion and damage, ischemia, and drug-induced liver injury[71,72] (Figure 3).

MOLECULAR FEATURES: HEPATOTROPISM OR HEPATIC FRAILTY

The specificity of the virus to preferably invade hepatocytes is considered hepatotropism[65,73-75]. According to current research, SARS-CoV-2 does not specifically display hepatotropism but shows a preference for hepatocytes in patients with a pre-existing liver disease or a compromised immune system[76,77]. Patients with an existing liver disease display severe and prolonged symptoms of SARS-CoV-2 because the immune system dysfunction displays a more pronounced effect[45]. A meta-analysis of 90000 patients with COVID-19 pertaining to 40 case studies in the United States and China provided strong evidence for hepatic deterioration[78]. Hepatic frailty makes liver cells more susceptible and sensitive to COVID-19[79,80]. COVID-19 and comorbidities of hepatic diseases is a global phenomenon

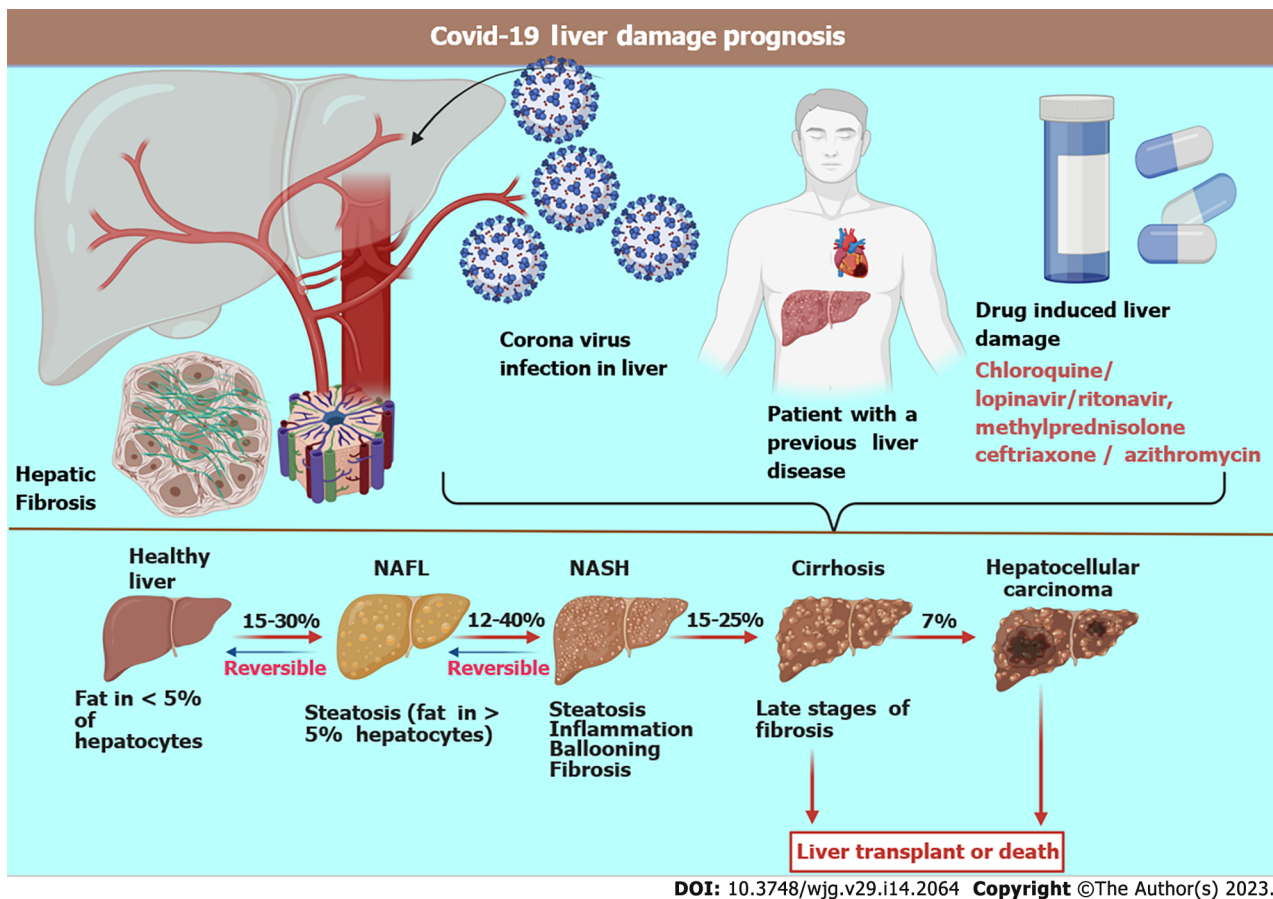


Figure 2 The schematic representation of the effects of severe acute respiratory syndrome coronavirus 2 on the liver. A patient with a pre-existing liver disorder exhibits higher morbidity than patients with normal liver. Drugs may cause liver damage in some patients, making treatments ineffective. The stages of disease progression are implicated as steatosis (deposition of fat), causing a nonalcoholic fatty liver. The liver deteriorates, indicated by inflammation, ballooning of hepatocytes, and fibrosis. Severe liver cirrhosis is the next stage, which is irreversible. The final stage is hepatic cancer. COVID-19: Coronavirus disease 2019; NAFL: Nonalcoholic fatty liver; NASH: Nonalcoholic steatohepatitis.

[80,81].

The invasion of SARS-CoV-2 virus in the human body, its genomic single-stranded RNAs, and the replicative double-stranded RNAs are sensed by cytosolic RNA sensors. These are then identified and bound to NOD-like receptors, endosomal toll-like receptors, melanoma differentiation-associated gene 5, and retinoic acid-inducible gene-I-like receptors[82]. These receptors then stimulate the next set of effectors molecules downstream interferon (IFN) regulatory factor 3/7 (IRF3/7); activator protein-1; and nuclear factor- κ B (NF- κ B). The next step encompasses the synthesis of pro-inflammatory cytokines, namely, interleukin (IL)-2, IL-10, IL-6, IL-8; and IFN-I, by activating their transcription. These IFN-I molecules are thus supposed to be the first line of defense to combat and clear the viral particles from the body; these thus induce signal transducer molecules the Janus kinase 1 (JAK1)/tyrosine kinase 2 and transcription 1/2 (STAT1/2), turning on the JAK1/TYK2-STAT1/2 pathway. This generates STAT1/2/IRF9 complex that additionally triggers the transcription of IFN-stimulated genes. Thus, a cascade of events leads to the massive synthesis of antiviral chemicals: Procalcitonin; IL-6, CCL-5, IL-1, IFN-alpha, CXCL10, and CXCL-8, C-reactive protein[83]. Many studies have hinted at the unconventional triggering of certain supplementary systemic inflammatory responses leading to uncontrolled immune responses signaled by a storm of cytokines produced due to the activation of NF- κ B and mitogen-activated protein kinase (MAPK) pathways[82]. This is commonly known as systemic inflammatory response syndrome, where a horde of immune cells (B cells, T-cells, natural killer cells, dendritic cells, neutrophils, and macrophages) bring about a cumulative and exaggerated response[84]. Apoptosis and cell death remain the culminating stage regulated by the MAPK pathway. Pyroptosis is a specialized mechanism induced by coronaviruses to prevent viral spread leading to an inflammatory caspase-1-dependent cell death in patients in response to rapid viral replication within infected cells[85]. In this activation process, the virus secures its persistence through the PI3 kinase/Akt pathway[86].

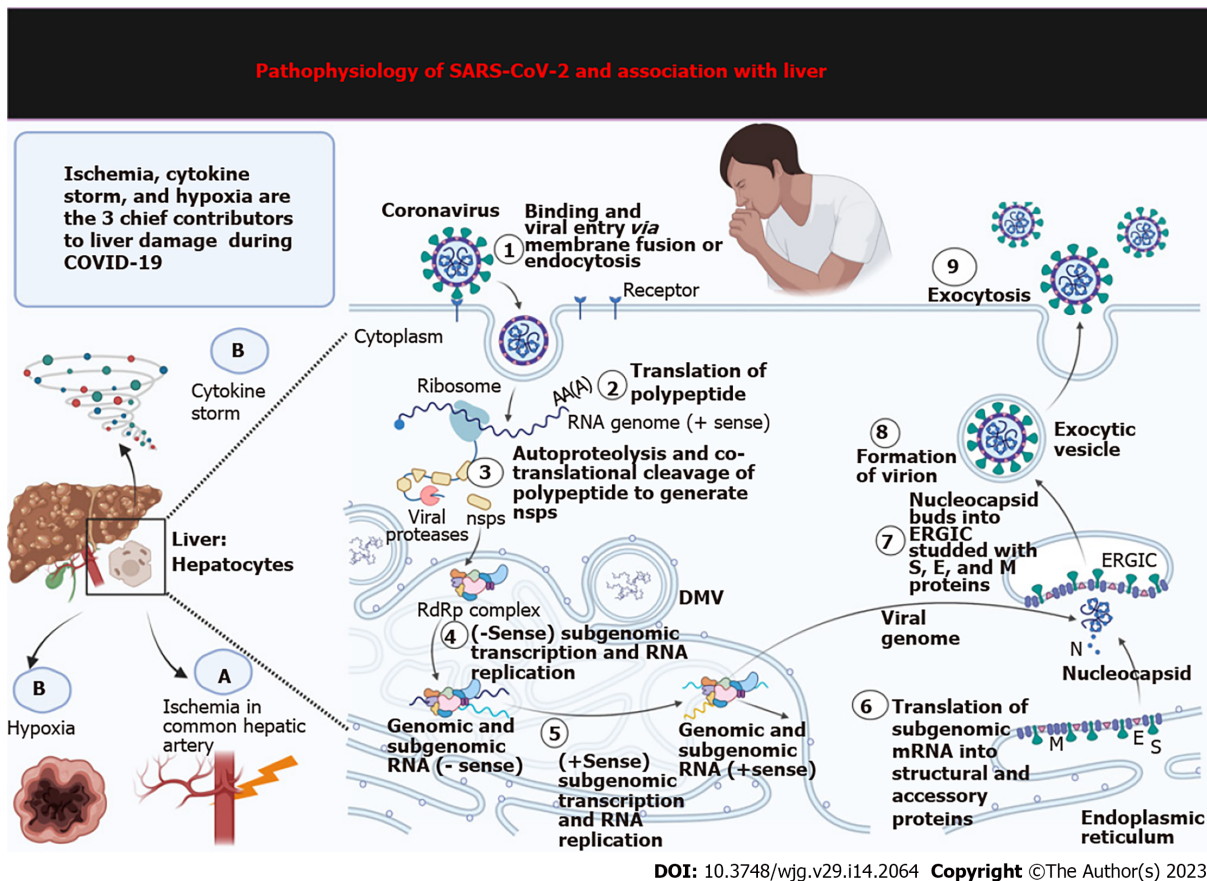


Figure 3 Molecular mechanisms of liver damage during coronavirus disease 2019 infection. Hypoxia, ischemia, and cytokine storm significantly contribute to liver damage in coronavirus disease 2019-related comorbidities. This figure depicts how severe acute respiratory syndrome coronavirus 2 exponentially proliferates after entering hepatocytes. The steps occur: (1) Binding and viral entry via membrane fusion or endocytosis; (2) Translation of polypeptide; (3) Autoproteolysis and cotranslational polypeptide cleavage to generate non-structural proteins (nsps); (4) Sense subgenomic transcription and RNA replication; (5) + Sense subgenomic transcription and RNA replication; (6) Translation of subgenomic mRNA into structural and accessory proteins; (7) Nucleocapsid buds into ER-Golgi intermediate compartment studded with spike, envelope, and membrane proteins; (8) Formation of virion; and (9) Exocytosis. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; ERGIC: ER-Golgi intermediate compartment; DMV: Double-membrane vesicle.

PHARMACOLOGIC THERAPIES SPECIFIC TO CORONA-ASSOCIATED HEPATIC MORBIDITIES

Scientists worldwide could conceive fairly early the devastating effects of SARS-CoV-2, and social distancing was the only way out since impending outcomes were far from the view[87,88]. As an opportunist virus, it intimidated the whole world, shutting down everyday life and hampering the economy and health worldwide. Though we have successfully tamed this dangerous and feral pathogen, the efficacy of existing vaccines and drug therapies in preventing SARS-CoV-2 variants is still a matter of concern[87-89]. Vaccines were tracked on the plan to target spike proteins of the SARS-CoV-2, which the virus variants inventively cons[90-92]. Several novel vaccines, as well as drugs, have ardently helped in tackling these viruses. Since the virus shows high transmissibility and the future modulation in these viruses is erratic and unforeseen[90,92,93], prevention and management strategies should entail a multi-omic, closed-loop follow-up and holistic approach comprising scientists, government authorities, clinicians, pharmacists, and as the general public. Thus, prevention and management, including pharmacologic therapies against COVID-19, have been worked out under different approaches certified under Emergency Use Authorization[94-96]. Several therapeutic strategies are followed depending on the patient's condition as diagnosed by the clinician[97,98].

Immuno-modulators and anti-inflammatory agents

More appropriate to provide in the later stage of COVID-19 infection. Clinical trials conducted on 113 COVID-19 patients critically suffering from this disease, with both Baricitinib (inhibitor of Janus kinase) and Anakinra (IL-1 antagonists on 52 COVID-19 patients), have shown promising results in the case of COVID-19 patients facing hyperinflammation (cytokine storm). These offer a dual inhibitory effect by preventing both entries of SARS-CoV-2 and preventing an exaggerated cytokine response[99-102]. Such trials have attested to the efficacy of critical-stage COVID-19 patients, especially those with hepatic

Table 2 Summary of the effective vaccines developed so far against coronavirus disease 2019

Sr. No.	Name of vaccine	FDA approval	Type of vaccine	Manufactured by	Efficacy	No. of doses	Safety profile	Ref.
1	NVX-CoV2373 vaccine	December 20, 2021	Recombinant SARS-CoV-2 nanoparticle	Novavax	92.6%	2	Safe till date	[105]
2	BNT162b2 vaccine	FDA issued a EUA on December 11, 2020	mRNA-based	BioNTech/Pfizer	95%	2	Safe till date	[106]
3	mRNA-1273 vaccine	FDA issued a EUA on December 18, 2020	mRNA-1273 based	Moderna	94.1%	2	Safe till date	[107]
4	ChAdOx1 nCoV-19 vaccine	Not yet received a EUA or approval from the FDA	Recombinant spike protein vaccine	Serum institute of India, private limited	70.4%	2	Vaccine-induced immune thrombotic thrombocytopenia	[108]
5	Ad26.COV2	EUA by the FDA on February 27, 2021	Recombinant vaccine	Janssen-Cilag International, NV Belgium	73.1%	1	Vaccine-induced immune thrombotic thrombocytopenia	[109]
6	Covaxin	EUA for adults	Whole inactivated virus-based	Bharat Biotech in collaboration with ICMR and NIV, India	64%	2	Safe till date	[110]
7	Sputnik V	EUA qualified	Human adenovirus vector	Russian direct investment fund	97.2%	2	Safe till date	[111]
8	CoronaVac	FDA issued under EUA	Inactivated virus alum-adsjuvanted candidate vaccine	Sinovac biotech, China	51% against symptomatic SARS-CoV-2 infection, 100% against severe COVID-19	2	Safe till date	[112]

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; FDA: Food and Drug Administration; EUA: Emergency Use Authorization; ICMR: Indian Council of Medical Research; NIV: National Institute of Virology.

complaints[103,104]. Table 2 shows the currently used effective vaccines developed and successfully reduced morbidity and mortality across the world[105-112].

Antiviral drugs

These are more suitable during the early phase of Corona infection. Molnupiravir, a very effective drug that reduces both morbidity and mortality; paxlovid: Reduced 89% mortality (trial conducted on 1219 patients); remdesivir, hydroxychloroquine, lopinavir/ritonavir, ivermectin, and chloroquine are all Food and Drug Administration approved, but show little or no effect over Coronavirus; it is even not effective against corona variants[113,114]. Therefore, they are not recommended in case of patients with hepatic trouble during COVID-19. Also, some of these drugs (lopinavir/ritonavir, mitofevir, and tocilizumab) are not recommended and prescribed to patients with pre-existing liver diseases as they are known to cause cholestatic toxicity and hepatic injury[115-117].

Neutralizing antibodies against SARS-CoV-2

Antibodies naturally produced by the body of recovering patients or stimulated through vaccination can block the attachment and hence the entry of an enveloped viral pathogen inside the cell, conferring lifelong immunity[118-121]. Convalescent plasma transfusion therapy with a high anti-SARS-CoV-2 immunoglobulin G (IgG) titer effectively lowered the mortality of critical COVID-19 patients[122-124]. The bamlanivimab and etesevimab antibody combination has been found to be super effective in COVID-19 patients with 87% lower death rate[125]. Another antibody cocktail, REGN-COV2, constitutes a group of two IgG1 antibodies (casirivimab and imdevimab) that target the receptor binding domain of SARS-CoV-2 and thereby reduce both morbidity and mortality of COVID-19 patients by 70%[126].

CONCLUSION

Extraordinary efforts have reaped fruits. As per the World Health Organization report on COVID-19 Vaccine Implementation Analysis & Insights, 63.4% of the World's population today stands vaccinated against COVID-19 in September 2022 (<https://www.who.int/publications/m/item/covid-19-vaccine-implementation-analysis-insights-2-september-2022>), and India alone proudly puts up 68% of its population in the list of a fully vaccinated cluster. This was made possible due to the untiring efforts of clinicians and researchers braced and heavily funded by the government and private agencies to curb this callous pandemic. It is anticipated that once 100% global vaccination is achieved, the virus will no longer be felonious. However, there are reasons to negate this notion. One explanation is that despite marshy governmental efforts, many people are vaccine-hesitant for inexplicable motives which may hamper virus block[127,128]. Even if this temper is somehow overcome, the dynamics of remodelling human immunity to ongoing viral mutations and evolution is worth consideration. The co-evolution may equip the virus with new immune strategies to escape the human immune defense mechanism and maintain its virulence. According to the United States Centres for Disease Control and Prevention, viruses with new mutations are specifically a matter of concern and shall not be considered lightly[128]. Lifestyle, access to wet markets, climate change, and increased animal-human interactions offer preferred gateways and richer niches to these evolving viruses[129]. The armchair experts in virology, immunology, and genetics contribute substantially to future mitigation strategies. It can no longer be one bug, one drug approach. Herd immunity is expectantly looked upon but is short-term and modulates the virus with new attacking feats. What is good to know is that though the future is unseen, this COVID-19 pandemic has taught us valuable lessons and equipped health agencies, clinical experts, and the general public to face the subsequent pandemic terror.

FOOTNOTES

Author contributions: Khullar N and Bhatti JS contributed equally, performed the majority of the writing, and prepared the figures and tables; Singh S and Thukral B performed data accusation and writing; Reddy PH provided input on writing the paper; Bhatti GK designed the outline and coordinated the writing of the paper; and all authors have read and approved the final manuscript.

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