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REVIEW

Intestinal barrier dysfunction as a key driver of severe COVID-19

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Abstract

The intestinal lumen harbors a diverse consortium of microorganisms that participate in reciprocal crosstalk with intestinal immune cells and with epithelial and endothelial cells, forming a multi-layered barrier that enables the efficient absorption of nutrients without an excessive influx of pathogens. Despite being a lung-centered disease, severe coronavirus disease 2019 (COVID-19) affects multiple systems, including the gastrointestinal tract and the pertinent gut barrier function. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can inflict either direct cytopathic injury to intestinal epithelial and endothelial cells or indirect immune-mediated damage. Alternatively, SARS-CoV-2 undermines the structural integrity of the barrier by modifying the expression of tight junction proteins. In addition, SARS-CoV-2 induces profound alterations to the intestinal microflora at phylogenetic and metabolomic levels (dysbiosis) that are accompanied by disruption of local immune responses. The ensuing dysregulation of the gut-lung axis impairs the ability of the respiratory immune system to elicit robust and timely responses to restrict viral infection. The intestinal vasculature is vulnerable to SARS-CoV-2-induced endothelial injury, which simultaneously triggers the activation of the innate immune and coagulation systems, a condition referred to as "immunothrombosis" that drives severe thrombotic complications. Finally, increased intestinal permeability allows an aberrant dissemination of bacteria, fungi, and endotoxin into the systemic circulation and contributes, to a certain degree, to the over-exuberant immune responses and hyper-inflammation that dictate the severe form of COVID-19. In this review, we aim to elucidate SARS-CoV-2-mediated effects on gut barrier homeostasis and their implications on the progression of the disease.

Key Words: COVID-19; SARS-CoV-2; Intestinal barrier; Dysbiosis; Immunothrombosis; Gut-lung axis

Core Tip: Severe coronavirus disease 2019 (COVID-19) is associated with a multi-layered disruption of gut barrier integrity. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) inflicts direct cytopathic or indirect immune-mediated injury to intestinal epithelial and endothelial cells and enhances paracellular permeability by downregulating tight junction proteins. SARS-CoV-2 induces profound gut microbiome alterations accompanied by dysregulation of mucosal immune responses. Gut dysbiosis attenuates, through the gut-lung axis, the ability of the respiratory immune system to elicit vigorous responses to contain SARS-CoV-2. Additionally, intestinal barrier dysfunction promotes endothelial activation and predisposes to detrimental COVID-19-related thrombotic complications. Finally, bacterial translocation and endotoxemia contribute to over-exuberant immune responses and hyper-inflammation in severe COVID-19.

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INTRODUCTION

The emergence of the novel, pathogenic, and highly transmissible severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), triggered an unprecedented public health crisis with profound socioeconomic sequelae. In most cases, COVID-19 is associated with mild-to-moderate symptoms that mainly involve the respiratory tract. However, in a subset of patients, COVID-19 may progress into a more severe disease plagued with complications such as pneumonia, acute respiratory distress syndrome (ARDS), coagulopathy, myocarditis, hepatic injury, renal dysfunction, sepsis, multiple organ failure, or even death[1]. These detrimental effects are considered to be driven by aberrant activation of the host's immune system in response to viral invasion and proliferation into the pulmonary parenchyma[2]. In particular, the virus-laden pneumonocytes secrete excessive amounts of pro-inflammatory mediators and chemoattractant molecules, such as interleukins (IL-1β, IL-6, IL-7, IL-8, IL-12), tumor necrosis factor alpha (TNF-α), interferons (IFN-γ, IFN-λ), macrophage inflammatory protein-1 alpha (MIP-1α), monocyte chemoattractant protein-1 (MCP-1), and granulocyte colony stimulating factor. Subsequently, the recruitment and activation of innate and adaptive immune cells into the lungs further aggravate tissue injury and inflammation[2]. In parallel, the systemic dissemination of this "cytokine storm" precipitates overactivation of the immune system beyond the sites of infection and elicits hyperinflammatory responses that impair the function of several organs including the heart, kidneys, liver, nervous system, and gastrointestinal (GI) tract[3].

The GI system harbors an enormous interface that directly communicates with the external environment of the body and fulfills multifaceted functions. The GI mucosa serves as a semi-permeable membrane, allowing the efficient absorption of water, electrolytes, and nutrients while, in parallel, preventing the influx of xenobiotics, intraluminal microbiota, microbial components, or other inflammatory stimuli into the organism[4]. This subtle balance is maintained thanks to intestinal barrier function, which, apart from providing a physical barrier, regulates complex immune system responses and mediates the intricate crosstalk with the gut microbiome[5]. The integrity of the intestinal barrier can be compromised in many acute or chronic pathological conditions, leading to increased bacterial translocation and excessive penetration of pro-inflammatory signals. This dysfunction is associated with infectious complications and the establishment of a systemic pro-inflammatory status that can exacerbate or accelerate the pathophysiological processes of the underlying disease[6].

In this review, we summarize the deleterious effects of SARS-CoV-2 infection on gut barrier homeostasis. Subsequently, we discuss the mechanisms that explain how intestinal barrier dysfunction might drive severe COVID-19 or induce detrimental complications.

GI INVOLVEMENT AND THE MECHANISMS OF INTESTINAL INFECTION IN COVID-19

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus with a genome of approximately 30000 nucleotides that encodes 29 proteins, including 4 structural proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E) proteins. The S protein consists of the S1 subunit, which interacts with angiotensin-converting enzyme 2 (ACE2), and the S2 subunit which promotes membrane fusion[7,8]. The principal route of transmission of SARS-CoV-2 is *via* respiratory droplets or aerosols

from person-to-person, and its main target is type II alveolar epithelial cells (AEC2s). The entry of SARS-CoV-2 is primarily mediated by the attachment of the S glycoprotein with ACE2 on the cellular surface, a process facilitated by proteolytic cleavage at the S1/S2 boundary by host proteins. Transmembrane protease serine 2 (TMPRSS2) is a significant host protease that mediates the cleavage of S2 protein, leading to conformational changes that precipitate viral entry through membrane fusion[7, 8]. Intriguingly, ACE2 and TMPRSS2 are widely co-expressed on the membrane of intestinal epithelial cells (IECs) at a level comparable or even higher to that of the AEC2s, rendering the GI tract a potential target for SARS-CoV-2 infection[9].

Multiple studies have demonstrated that the development of GI-related symptoms is a common extrapulmonary manifestation, affecting up to one-fifth of patients with COVID-19[10-12]. According to a meta-analysis of 108 studies comprising 17776 COVID-19 patients, the pooled prevalence estimates of GI symptoms were: 21% for loss of appetite, 13% for diarrhea, 8% for nausea or vomiting, and 4% for abdominal pain, while derangement of liver function tests was observed in 24% of the participants[10]. Whether the occurrence of GI symptoms is associated with COVID-19 severity or outcomes has been a field of debate. Most meta-analyses support that GI-symptoms and predominantly abdominal pain tend to appear at higher rates among patients with severe disease[10,13-15]; however, these symptoms are not always predictive of mortality or intensive care unit (ICU) admission[16-18]. Importantly, viral RNA can be detected in the stool of about half of COVID-19 patients and, especially, in those with GI-related symptoms[19,20]. Viral rectal shedding appears to persist long after RNA clearance in respiratory samples (mean duration: 21.8 d *vs* 14.7 d)[20], while RNA concentration in the stool may be as high as 10^7 copies/g, exceeding even that in pharyngeal swabs in some cases[21]. The combination of this particularly high RNA load in the stool and the long-lasting viral presence in fecal samples strongly suggests that SARS-CoV-2 invades and proliferates in the intestinal tract. Indeed, COVID-19 elicits acute inflammatory responses in the gut, as documented by increased fecal calprotectin levels[22]. Accordingly, Livanos *et al*[18] provided direct evidence of direct infection of IECs by SARS-CoV-2 *in vivo*, using immunofluorescence staining and electron microscopy. Viral subgenomic mRNA (sgmRNA) is transcribed in infected cells, but is not encapsulated into virions, which means that sgmRNA is vulnerable to enzymatic degradation by intestinal ribonucleases. Therefore, the detection of sgmRNA in the stool of COVID-19 patients also indicates that the virus can actively and specifically replicate in the gut[21].

Although the data above corroborate the concept of SARS-CoV-2 tropism for the GI system, the routes and mechanisms of infection remain less clarified. At least theoretically, the feasibility of the fecal-oral route of transmission is supported by prolonged viral excretion in the feces. Nevertheless, although SARS-CoV-2 retains viability in stool for 1-2 d at room temperature, this is accompanied by a profound 5-log loss of its infectivity[23]. In addition, ingested SARS-CoV-2 needs to overcome the harsh gastric acidity, resist the detergent effects of bile acids in the duodenum, and avoid degradation by digestive enzymes to preserve its infectivity and spread into the intestinal epithelia[24]. The uninterrupted function of these host defense mechanisms hinders the fecal-oral transmission of enveloped viruses, such as SARS-CoV-2[25]. Besides, several lines of evidence support that intestinal infection by SARS-CoV-2 could occur *via* the bloodstream[19,26]. The virus replicating in pulmonary alveolar epithelial cells or in ciliary cells of the nasal cavity is capable of breaching the basement membrane and causing viremia[27]. The GI tract comprises an extended network of capillaries harboring vascular epithelial cells, which are potential targets of circulating SARS-CoV-2. Thereafter, the proliferating virus is released from the infected cells into the gut, where it can infect neighboring enterocytes or reenter the circulation to generate new cycles of infection[27,28].

THE INTESTINAL BARRIER FUNCTION IN HEALTH

The gut barrier function is equipped with three major lines of defense that conjointly serve its complex purpose[5]. First, the mechanical barrier consists of tightly linked columnal IECs, the overlying mucus layer, and the capillary endothelial cells of the submucosa[29]. Tight junctions (TJs) and adherens junctions (AJs) are transmembrane multiprotein complexes that confer structural stability to the mechanical barrier and engender the establishment of cell polarity. TJs connect the most apical of the lateral surfaces of the adjacent epithelial or endothelial cells (kissing points) and form channels that regulate the selective diffusion of ions and salutes through the paracellular space. AJs are more basal than TJs and contribute to the establishment and maintenance of cell-cell adhesion[30,31]. The mucus layer comprises a hydrated network of polymers, predominantly highly glycosylated mucin proteins, as well as several immune regulators, such as antimicrobial proteins (AMPs) and secretory immunoglobulin A molecules. The mucus lubricates the luminal contents and serves as a physical barrier against digestive enzymes, proliferating microorganisms, microbial components and byproducts, food-associated toxins, or other inflammatory stimuli[32]. In addition, it nurtures a thriving biofilm of microorganisms, the gut microbiome, which typifies the second mechanism of protection, the biological barrier[29,32]. Luminal microbiota are indispensable for the fermentation of indigestible carbohydrates, a process that provides the gut with short-chain fatty acids (SCFAs), mainly consisting of acetate,

propionate, and butyrate. Apart from being an important source of energy for host cells, SCFAs exhibit significant anti-inflammatory and anti-tumor effects and participate in various host signaling pathways, contributing to intestinal barrier integrity and metabolic homeostasis The commensal bacteria regulate choline bioavailability, promote the enterohepatic circulation of bile acids, and synthesize vitamin K and group B vitamins. In parallel, normal intestinal flora restrains the overgrowth of harmful microorganisms, a phenomenon referred to as colonization resistance, through nutrient antagonism[33]. Moreover, the microbiome-derived pathogen-associated molecular patterns (PAMPs) are recognized by pattern recognition receptors (PRRs) expressed by intestinal immune cells, indicating a relentless reciprocal dialogue between the microbiota and the intestinal immune system[6]. This leads to the third line of defense, that is, the immune barrier, which encompasses the gut-associated lymphoid tissue (GALT), effector and regulatory T cells (Tregs), immunoglobulin A (IgA)-secreting B (plasma) cells, innate lymphoid cells (ILCs), as well as macrophages and dendritic cells (DCs) of the lamina propria[5]. The cells of innate immunity carry an armamentarium of PRRs such as toll-like receptors (TLRs), nucleotide oligomerization domain-like receptors (NLRs), and retinoic acid-inducible gene-like receptors (RLRs) that recognize molecular pathogen-associated molecular patterns (PAMPs) or damaged-associated MPs (DAMPs) and orchestrate the well-tuned responses of the adaptive arm of the immune system.

The continuous crosstalk of the immune cells with the gut microbiome sustains the delicate balance between tolerance to beneficial bacteria and immunosurveillance against pathogenic species[6]. Commensal-derived signals and metabolites are recognized by myeloid cells in the lamina propria and orchestrate innate and adaptive immune responses[34]. Under homeostatic conditions, innate immune cells, such as macrophages and DCs, obtain a regulatory phenotype that promotes the secretion of anti-inflammatory molecules, *i.e.*, IL-10 and TGF-β. The production of IL-22 by type 3 ILCs supports tissue homeostasis and epithelial barrier integrity[35]. Properly-regulated antigen presenting cells (APCs) remain in the GALT or migrate to the mesenteric lymph nodes, where priming of naïve CD4+ T cells occurs, and stimulate Treg cell activity that plays a central role in the suppression of intestinal inflammation. In this immunomodulatory milieu, B cell activation and effective class-switching generate large numbers of IgA-secreting plasma cells that serve multiple functions, including protection against infection and maintenance of gut microbiome homeostasis[35].

THE INTESTINAL BARRIER FUNCTION IN COVID-19

SARS-CoV-2 disrupts the intestinal mechanical barrier

SARS-CoV-2 can invade and propagate in IECs by using the vastly expressed ACE2 and TMPRSS2 receptors on those cells[18,36]. In a mouse model, ACE2 was found to be a key inducer of intestinal stem cell proliferation and differentiation under pathologic conditions, while ACE2 deficiency was associated with a significant reduction of mucin-2 expression[37]. Accordingly, ACE2 knockout mice exhibited gut barrier dysfunction with subsequent leakage of bacterial components into the circulation[38]. Therefore, it could be hypothesized that interference of SARS-CoV-2 with ACE2 signaling could destabilize the mechanical barrier by interrupting the renewal of epithelial cells or by compromising mucus composition. Mucins create a protective matrix covering the epithelium and inhibit viral invasion, presumably *via* steric hindrance[39]. Even though evident macroscopic alterations were usually negligible, infection of the human small bowel by SARS-CoV-2 was associated with villi blunting and an aberrant accumulation of activated intraepithelial CD8+ T cells in the epithelium[36]. Cell trafficking could be driven by direct infection of IECs or could be the result of systemic immune activation due to COVID-19. In any case, the recruitment of intraepithelial CD8+ T cells enhanced the apoptotic process of IECs, as demonstrated by an upsurge in cleaved caspase-3+ apoptotic epithelial cells. This event was accompanied by a regenerative response of the epithelium marked by an increase in Ki67+ proliferating epithelial cells that extended beyond their typical localization in the crypts and occupied the villus compartment[36]. Evidently, SARS-CoV-2 can inflict a deleterious impact on the mechanical barrier through dysregulation of the balance between cell apoptosis and proliferation.

The function and integrity of epithelia and endothelia greatly depend on TJs, reflecting a putative mechanism of intestinal barrier injury in COVID-19 patients. The fundamental transmembrane proteins that frame TJs include the family of claudins (central regulators of paracellular permeability encompassing 26 members in humans), the junctional adhesion molecules, and the three junctional MARVEL domain proteins, *i.e.*, occludin, tricellulin, and MARVEL domain-containing protein 3. The most prominent intracellular junctional plaque components are zonula occludens (ZO) proteins (ZO1, ZO2, and ZO3), cingulin, and protein associated with LIN7 1 (PALS1)[40]. These proteins function as adaptor proteins or cytoskeletal linkers and participate in multiple extracellular and intracellular signaling pathways. Indeed, impairment of TJs occurs early in the course of COVID-19 and might represent the first hit in a multistage model of the disease[41]. SARS-CoV-2 infection decreases the expression of TJ proteins, such as occludin, claudin 5, and ZO-1 *in vivo*, and undermines the coherence of TJs between neighboring endothelial cells of the brain. As a result, TJs are haphazardly distributed, irregular, or gapped throughout the vascular endothelial layer, leading to derangement of the function

of the blood-brain barrier[42]. Cryo-electron microscopy and *in silico* modeling analyses have shown that SARS-CoV-2 uses its envelope (E) protein to interact with the TJ-associated PALS1 protein[43,44]. According to *in vitro* models of lung injury, the interplay between SARS E protein and PALS1 interrupts intracellular trafficking of E-cadherin, delays the formation of TJs and AJs, and affects epithelial polarity [45]. In a proof-of-concept study, Guo *et al*[46] developed a biomimetic human gut-on-chip model that reconstructs basic elements of the gut barrier, as it consists of IECs, endothelial, and mucin-producing cells under normal fluid flow and closely reproduces the pathophysiological processes of intestinal SARS-CoV-2 infection. Interestingly, IECs exhibit particularly high susceptibility to SARS-CoV-2 infection. Viral inoculation induces the dispersal of the physiological distribution of mucus-secreting cells and a profound reduction of both E-cadherin expression in the epithelium and VE-cadherin in the endothelium, which delineate serious impairment of AJs in the corresponding structures. As a consequence, widespread destruction of the villus-like complexes along with severe morphological remodeling of the vascular endothelium was observed[46]. IL-6 is a prominent mediator of inflammation and a reliable biomarker of disease severity in SARS-CoV-2 infection that was found to increase, in a sustained manner, endothelial permeability in a mouse model[47,48]. Administration of IL-6 induced vascular leakage and disruption of junctional localization of VE-cadherin and ZO-1 *via* Janus kinase-mediated signal transducer and activator of transcription 3 phosphorylation and *de novo* protein synthesis[48].

Serum levels of endotoxin and ZO-1 were significantly increased in patients with COVID-19-related pneumonia on admission compared to healthy controls. Importantly, endotoxemia is positively correlated with certain markers of inflammation, such as C-reactive protein (CRP) and ferritin[49]. Endotoxins are complex lipopolysaccharides (LPS), integral parts of the membrane of gram-negative bacteria, and potent drivers of inflammation. Indeed, endotoxemia can occur as a result of gram-negative bacteremia; however, endotoxemia is most commonly caused by a compromised gut barrier [50]. ZO-1 is a peripheral membrane scaffolding protein and a basic constituent of TJs that fulfills versatile functions including establishment of cell-cell adhesion, modulation of the paracellular barrier, regulation of cell migration and angiogenesis, and induction of mucosal repair processes[51,52]. Previous studies have confirmed that serum ZO-1 represents a reliable biomarker of disrupted paracellular permeability, as it inversely correlates with intestinal ZO-1 expression in diverse pathologic conditions[53,54]. These results are consistent with another study, in which severe SARS-CoV-2 infection presented key features of gut barrier dysfunction *in tandem* with increased intestinal permeability. Specifically, patients with severe COVID-19 presented with endotoxemia and higher serum levels of zonulin, occludin, and regenerating family member 3 alpha, indicating severe impairment of the intestinal epithelial barrier[55].

SARS-CoV-2-induced gut microbiome dysbiosis

In the course of evolution, hosts and their microbial ecosystems have mutually developed, forging an intimate relationship of interdependence. Dysbiosis refers to alterations in the composition, quantity, or distribution of the gut microbiome. This condition is characterized by a predominance of pathogenic species and has been linked to the pathophysiology of numerous intestinal and extraintestinal disorders [56]. There is a growing body of data suggesting that COVID-19 is associated with drastic alterations of the normal intestinal flora, even when removing the confounding effect of antibiotics (Figure 1)[57-59]. In addition, SARS-CoV-2-induced dysbiosis appears to persist long after the resolution of symptoms and might be a predisposing factor for long-term complications in COVID-19 patients[57,58,60].

The mechanisms underlying COVID-19-related dysbiosis have not yet been fully elucidated. The interactions between SARS-CoV-2 and the ACE2 receptor can influence the composition of gut microbiota by interfering with the secretion of AMPs. The activity of the amino acid transporter B^0AT1, which mediates the intestinal uptake of tryptophan, depends on ACE2 signaling[61]. Tryptophan regulates AMP production through the mammalian target of rapamycin pathway[62]. Therefore, tryptophan depletion due to ACE2 blockade can interrupt AMP production, and thus, perturb the intraluminal microbial community. Commensal bacteria, in turn, contribute to mucosal homeostasis by regulating ACE2 expression in the gut[63]. The release of pro-inflammatory cytokines, particularly TNF-α, during respiratory infections has a powerful anorexigenic effect *via* hypothalamic action. The ensuing reduction in caloric intake and dietary fibers disturbs the composition of the gut microbiota and the production of their metabolites. In animal models of respiratory syncytial virus (RSV) and influenza infection, the neutralization of anorexigenic cytokines prevented weight loss and mitigated gut microbiome alterations[64]. Alternatively, SARS-CoV-2 infection can cause dysbiosis through an imbalance of systemic or intestinal IFNs[65]. In this regard, in an influenza mouse model, the microbiome was amenable to significant changes *via* an IFN-type I-dependent mechanism[66]. Hypoxia is a serious feature of severe COVID-19 and hypoxic stress could be an important instigator of dysbiosis by dysregulation of hypoxia-inducible factor signaling[67]. Finally, local epithelial injury, which results in leaky gut and DAMP secretion, might disrupt the immune control of microbial homeostasis and could further aggravate the dysbiotic state[68].

In their recently published meta-analysis, Farsi *et al*[69] offered a thorough synthesis of the gut microbiota changes in COVID-19 patients. At the phylum level, dysbiosis is typified by a decrease in the *Firmicutes* to *Bacteroidetes* ratio. More specifically, COVID-19 is associated with a decrease in important

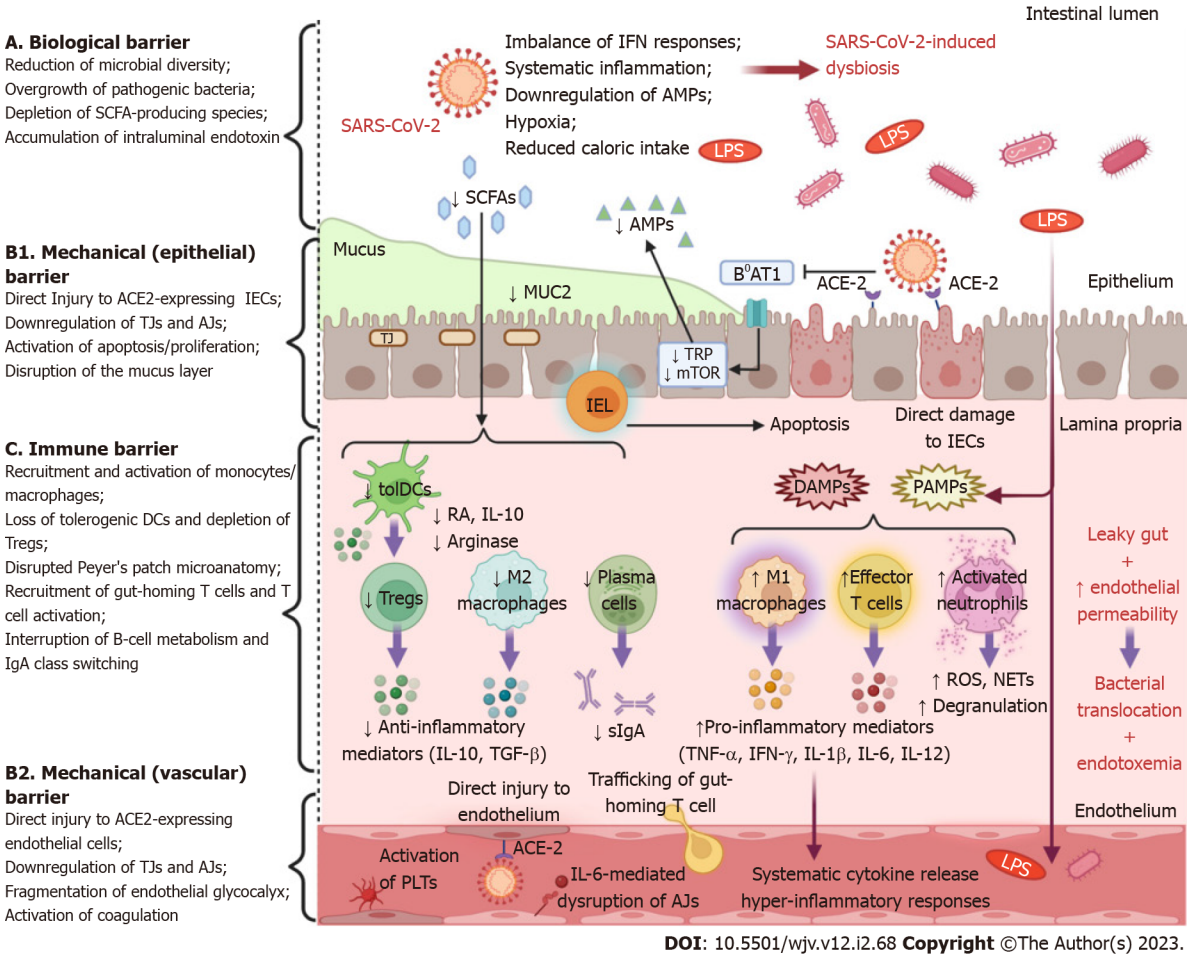

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Figure 1 Schematic representation of intestinal barrier dysfunction in severe acute respiratory syndrome coronavirus 2 infection. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with a multifaceted dysfunction of the gut barrier as it exerts detrimental effects on all of its major levels of defense. A: Systemic inflammation, an imbalance of interferon (IFN) responses, hypoxia or low blood flow, and reduced caloric intake, due to coronavirus disease 2019-associated cachexia, contribute to intestinal microbiome alterations. Gut dysbiosis is characterized by an overgrowth of opportunistic pathogens, which are a source of harmful substances, *e.g.*, endotoxin, peptidoglycan, β-glucan, as well as a depletion of commensal microorganisms, which synthesize beneficial metabolites such as short-chain fatty acids; B: SARS-CoV-2 induces either direct cytopathic injury to angiotensin-converting enzyme 2 (ACE2)-expressing intestinal epithelial cells (IECs) and endothelial cells, or indirect immune-mediated damage, or both. Moreover, the secretion of mucin glycoproteins, the fundamental element of the mucus layer, is severely impaired. In addition, the virus undermines the expression of tight junction and adherens junction proteins, leading to increased paracellular permeability and structural destabilization of the epithelium and endothelium. Viral interference with ACE2 signaling attenuates the activity of the amino acid transporter B0AT1, which is necessary for intestinal absorption of tryptophan (TRP). As a result, TRP depletion downregulates the mammalian target of rapamycin pathway, which promotes the expression of antimicrobial peptides. The overwhelming intraepithelial CD8+ lymphocytes trigger the apoptosis of IECs, which is followed by reactive regeneration. In parallel, disease-activated and apoptotic endothelial cells are potent drivers of neutrophil/monocyte recruitment, platelet aggregation, and coagulation activation; C: Commensal-derived metabolites modulate innate immune responses by inducing tolerogenic dendritic cells and M2-polarized macrophages. SARS-CoV-2-induced dysbiosis eliminates these immunoregulatory effects, inhibits T regulatory (Treg) cell activity, and suppresses the secretion of anti-inflammatory cytokines such as interleukin 10 (IL-10) and transforming growth factor beta. The release of damage-associated molecular patterns from injured cells and the influx of pathogen-associated molecular patterns, as a result of leaky gut, orchestrate the recruitment and activation of innate immune cells that secrete pro-inflammatory mediators (IFN-γ, tumor necrosis factor alpha, IL-1β, IL-6, IL-12). Subsequently, this pro-inflammatory microenvironment precipitates the derangement of adaptive immune responses, as demonstrated by increased trafficking of gut-homing T cells and effector T cell predominance. Furthermore, interruption of B-cell metabolism, plasma cell differentiation, and immunoglobulin A (IgA) class switching impede the effective secretion of protective dimeric IgA. This multi-layered disruption of intestinal barrier integrity allows the dissemination of intraluminal bacteria and endotoxin into the mesenteric lymphatic vessel or/and into the systemic circulation (created with biorender.com). IEL: Intraepithelial lymphocyte; LPS: Lipopolysaccharides; MUC2: Mucin 2; NETs: Neutrophil extracellular traps; PLTs: Platelets; RA: Retinoic acid; ROS: Reactive oxygen species; sIgA: Secretory immunoglobulin A; SCFAs: Short-chain fatty acids.

butyrate-producing bacteria, including *Faecalibacterium* and *Roseburia*[69-71]. The genus *Roseburia* contributes to mucosal integrity and colonic motility and exerts significant anti-inflammatory effects by modulating IL-10 production[72]. Similarly, *Faecalibacterium prausnitzii* is a valuable gut symbiont with recognized anti-inflammatory effects in IBD patients *via* inhibition of the nuclear factor kappa B pathway[73]. The gut microbiome of COVID-19 patients is also depleted of several other beneficial genera such as *Alistipes*, *Eubacterium*, and *Bifidobacterium*[69]. The genus *Eubacterium* consists of a phylogenetically diverse group of SCFA-producing bacteria that contribute to bile acid metabolism and exhibit compelling associations with intestinal health[74]. *Bifidobacterium* strains prompt Treg responses, induce tolerogenic DC phenotypes, and demonstrate vigorous antimicrobial and antiviral activity[75].

Of note, their ability to suppress gut dysbiosis and promote mucosal homeostasis has paved the way for researchers to investigate the therapeutic efficacy of *Bifidobacterium*-based probiotic preparations in several diseases, including irritable bowel syndrome, inflammatory bowel disease (IBD), or COVID-19 [76-78]. On the other hand, the COVID-19-derived gut microbiome is relatively enriched in opportunistic pathogens such as *Streptococcus*, *Bacteroides*, *Rothia*, *Veillonella*, *Actinomyces*, and *Eggerthella* [69,70]. Although the genus *Ruminococcus* is generally underrepresented, certain species such as *Ruminococcus gnavus* and *Ruminococcus torques* are significantly more abundant in COVID-19 patients. This is not surprising considering that *Ruminococcus gnavus* and *Ruminococcus torques* are harmful bacteria that degrade mucin glycans to harvest energy, secrete pro-inflammatory mediators, and are involved in IBD pathogenesis[79,80].

The degree of microbiome alterations correlates well with COVID-19 severity, and identification of early patterns of dysbiosis could lead to a microbiome-based stratification of patients according to their risk of progressing to severe COVID-19[81]. Indeed, the commensal genera *Faecalibacterium* and *Roseburia* are depleted in the gut microbiome of patients with critical disease[57,82]. The baseline abundance of *Clostridium ramosum* and *Clostridium hathewayi* is also associated with COVID-19 severity and could represent risk factors for portal vein thrombosis[69,82]. The genus *Enterococcus* is overrepresented in COVID-19 patients who necessitate ICU admission or developed bloodstream infections, whereas, surprisingly, the gut microbiome of other critically ill non-COVID-19 patients is devoid of this bacterium[83]. The reduction of the *Firmicutes*/*Bacteroidetes* ratio is indicative of severe disease, which is mainly attributed to the depletion of fiber-utilizing bacteria, namely *Faecalibacterium prausnitzii*, *Phocaeicola plebeius,* and *Prevotella*[84]. These findings are consistent with an interesting study exploring the role of gut microbiota as predictors of disease severity[81]. A lower *Firmicutes*/*Bacteroidetes* ratio, a higher prevalence of *Proteobacteria,* and an exhaustion of commensal butyrate-producing microorganisms are more evident in severely ill patients, while a lower bacterial diversity, defined by the Shannon diversity index, is identified as a prognostic biomarker of disease severity[81]. In agreement with this, the fecal microbiome of patients requiring mechanical ventilation has demonstrated low bacterial richness as assessed by Shannon or Chao1 indices[81,85,86]. Implementation of a multiomics approach to decipher the dysregulation of metabolic and microbial signatures during COVID-19 could provide a basis for the development of novel microbiome-targeted therapeutics[87].

SARS-CoV-2 deranging mucosal immune system responses

The mucosal immune system is the largest immunologically aware organ in the body, committed to maintaining the equilibrium between active protection against pathogens and immune-tolerance to commensal microorganisms, dietary substances, and self-antigens. The gut-derived metabolites orchestrate immune cell responses and differentiation and impart a critical role in mucosal homeostasis [56,88]. In particular, the transcriptional "education" of innate immune cells is strongly influenced by intestinal microbiota metabolites[56]. Butyrate, for example, induces M2-like polarization of macrophages, which shapes an immunomodulatory milieu by increasing the expression of arginase 1 and suppressing TNF-α, IL-6, IL-12b, and nitric oxide synthase 2[89]. As regards adaptive immunity, butyrate enhances transcription of the forkhead box P3 gene in naïve T cells through inhibition of histone deacetylases, and thereby, expands Treg cell populations[90]. The capsular polysaccharide A, which originates from the prominent human symbiont *fragilis*, promotes the proliferation of Treg cells in the lamina propria and shapes a pro-inflammatory microenvironment rich in IL-10[91]. Vitamin A or RA, produced by the gut commensal *Bifidobacterium infantis*, enhances the expression of aldehyde dehydrogenase 1 family member A2 encoding retinal dehydrogenase 2 in resident DCs of the mucosa. Subsequently, gut-modulated DCs secrete high levels of RA that drive naïve T cell differentiation into Treg cells[92]. Treg cell generation in the intestinal mucosa is also triggered by β-glucan polysaccharides deriving from the cell surface of *Bifidobacterium bifidum*[93]. In addition, B cell metabolism and differentiation in mucosal and systemic tissues are regulated by gut-derived SCFAs, emphasizing the significance of symbionts in effective antibody production[94]. Apparently, the depletion of SCFA-producing microorganisms or other beneficial species as well as gut metabolome modifications might have a detrimental impact on mucosal immunity in the course of COVID-19.

Defensins are prominent members of the AMP family with multifaceted immunomodulatory functions and broad antimicrobial and antiviral activity. Defensins provide protection against SARS-CoV-2 infection not only by maintaining gut microbiome homeostasis but also by inhibiting viral fusion *via* interference with ACE2 receptors[95,96]. Dysregulation in the expression of various defensin genes was evident following infection with COVID-19[97]. IFNs are multipotent cytokines of innate immunity with crucial role in the containment of viral infections. The proliferation of SARS-CoV-2 in human gut cells is effectively inhibited by type I (IFN-α, IFN-β) and type III IFNs (IFN-λs); however, type III IFNs elicit a more profound and long-lasting antiviral effect[98,99]. In order to escape immune surveillance, SARS-CoV-2 has developed strategies to proliferate stealthily into cells without eliciting strong IFN responses[65]. Alternatively, SARS-CoV-2 can interfere with IFN-γ (type II IFN) signaling to boost its infectively in the gut. In human colonic organoids, IFN-γ drives cellular differentiation towards ACE2-expessing epithelial cells, which are highly susceptible to SARS-CoV-2 infection[100]. Moreover, IFN-γ acts synergistically with TNF-α to instigate inflammatory cell death and tissue damage[101].

Elevated levels of plasma markers of inflammation and immune activation are hallmarks of severe COVID-19. Similarly, the expression of genes encoding pro-inflammatory mediators, including TNF-α, IL-6, chemokine (C-C motif) ligand 5 (CCL5), chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL10, CXCL11, and CSF-3 were upregulated in digestive tissues in both *in vitro* and *in vivo* models of SARS-CoV-2 infection[46,102]. Compared to uninfected individuals, patients with COVID-19 have increased fecal levels of pro-inflammatory cytokines such as IL-8 and IL-18, whereas IL-23 is higher in patients with severe disease[103,104]. Strikingly, analysis of human ileal biopsies has demonstrated that several pro-inflammatory genes including *IFNG*, *CXCL8*, *CXCL2*, and *IL1B* are downregulated. This pro-inflammatory response is associated with milder symptoms and improved outcomes, revealing an immunomodulatory function of the GI in controlling SARS-CoV-2 infection[18]. Nevertheless, molecular events in severe COVID-19, due to increased bacterial translocation and systemic immune activation, might eliminate the immunoregulatory functions of the GI. Indeed, post-mortem evaluation of COVID-19 patients' intestinal tissues revealed the overexpression of TNF-α and IL-10, which exerts antithetical effects[105]. The presence of IL-10 in the gut and lung may have immunosuppressive effects by inhibiting the expression of the human leukocyte antigen DR isotype (HLA-DR) on APCs[105]. Depletion of HLA-DR expression on monocytes is a major characteristic of immune dysregulation in COVID-19 patients who develop severe respiratory failure[106].

Essentially, changes in the expression of cytokines and downstream dysregulation of their signaling networks mirror alterations in the composition of immune cell populations of the lamina propria. Imaging mass cytometric analysis showed that the intestinal tract of deceased patients with COVID-19 accommodated higher numbers of CD11b+ macrophages, CD11c+ DCs, natural killer T cells, and B cells compared to healthy controls[105]. Another study, which evaluated post-mortem tissues of COVID-19 patients, demonstrated severe disorganization of ileal Peyer's patches with loss of B cell/T cell zonation and depletion of the germinal center. In addition, impaired interactions between B and T cells, an enhanced number of follicular macrophages, the reduction of CD27+ memory B cells, and downregulation of CD74 expression on B cells were reported[107]. Livanos *et al*[18] in their study, which supports an anti-inflammatory function of the GI in SARS-CoV-2 infection, showed that the lamina propria of COVID-19 patients was depleted of conventional DCs and plasmacytoid DCs, whereas effector CD4+ and CD8+ T cells as well as tissue resident memory T cells were increased. Lehmann *et al*[36]. revealed that the activation and proliferation of antigen-experienced intraepithelial CD8+ T cells into the intestinal mucosa was associated with epithelial barrier dysfunction in COVID-19 patients, while monocytes and macrophages of the duodenal mucosa expressed markers indicative of their recent recruitment from the circulation. In agreement, levels of CCL25, a gut homing marker, were increased in the sera of COVID-19 patients, suggesting that intestinal inflammation might result from CCL5/CCR9-mediated trafficking of gut-specific T cells into the mucosa[108,109]. Humoral immune responses are vital for counterattacking viral invasion through the production of neutralizing antibodies. Secretory dimeric IgA is the predominant mucosal antibody and an integral component of the immunological barrier[6]. IgA antibody overproduction dominates the early pre-specific humoral response to SARS-CoV-2 infection, while virus-specific IgA antibodies display more robust neutralizing capacity compared to their monomeric IgG counterparts[110]. Interestingly, the levels of mucosal SARS-CoV-2-specific IgA are inversely correlated with age[111]. Therefore, it can be inferred that the inability of B cells to mount an effective IgA response contributes to excessive viral propagation in the course of severe COVID-19[112].

THE GUT-LUNG AXIS IN COVID-19

As mentioned above, homeostasis of the gut microbiome can be immensely affected in the course of respiratory tract infections such as COVID-19. Conversely, intestinal microbiota plays an important role in fine-tuning the systemic immune system and eliciting efficient antiviral responses to address lung infections[113-115]. Gut bacterial components and metabolites can enter portal circulation or mesenteric lymphatics, which drain to the cisterna chyli first, then to the thoracic duct, and finally to the left subclavian vein. Intriguingly, the pulmonary vascular bed is the first to interact with the mesenteric lymph, implicating the importance of gut-derived signals in shaping lung immune responses in health as well as in driving ARDS in critically ill patients[116]. Under normal conditions, commensal-associated stimuli provide an indispensable for optimal antiviral activity, tonic activation of the host's innate immunity through their impact on alveolar macrophages, resident DCs, and lung epithelial cells (Figure 2)[117]. In contrast, germ-free mice are unable to evoke strong innate and adaptive immune responses and, thus, experience feeble control of viral infections and unfavorable outcomes[117,118]. Although the intestinal and respiratory tracts are anatomically distinct compartments, their mucosal immune cells and microbial communities configure a bidirectional "gut-lung" axis cross-talk that is highly pertinent to COVID-19 pathogenesis.

The mechanisms through which intestinal flora reinforces lung resilience against viral invasion have only recently begun to be unraveled with the assistance of murine models. The gut microbiota orchestrates the steady-state IFN signature in lung stromal cells, which protects against early influenza virus

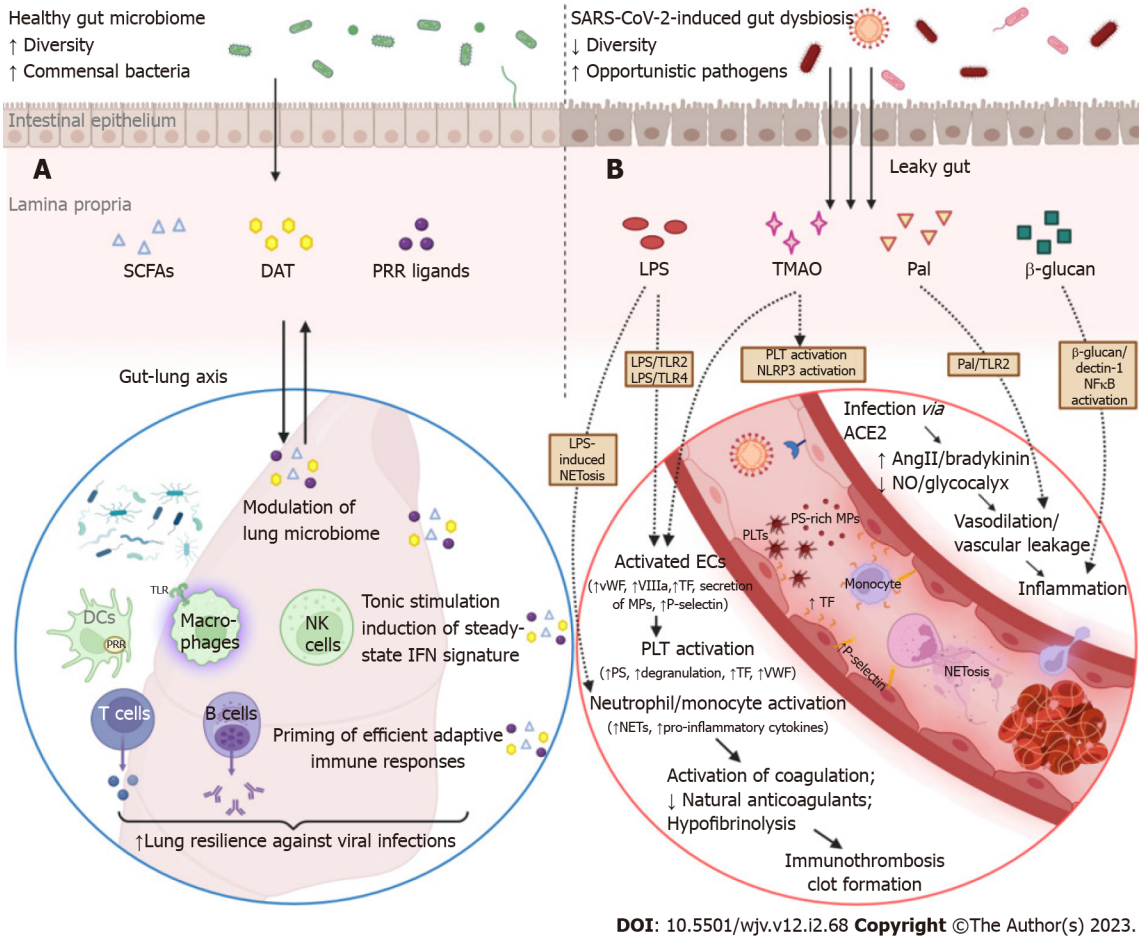

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Figure 2 Overview of the sequelae of gut barrier dysfunction in severe coronavirus disease 2019: dysregulation of lung immune responses and establishment of a prothrombotic state. A: Although the intestinal and respiratory tracts are anatomically distinct compartments, their mucosal immune cells and microbial ecosystems participate in a bidirectional immunological crosstalk (gut-lung axis). An intact intestinal barrier is pivotal in maintaining lung microbiome homeostasis and fine-tuning the respiratory immune system to elicit potent antiviral responses in the case of infection. Commensal bacteria provide tonic stimulation (through the production of pattern-recognition receptor-ligands, desaminotyrosine, short-chain fatty acids, *etc.*) of the epithelial, stromal, and innate immune cells of the lungs and modulate the steady-state interferon-signature, which is essential for suppressing the early phase of viral proliferation. In addition, gut-derived signals and metabolites orchestrate the effective priming of adaptive immune responses by inducing the differentiation of virus-specific CD4+ and CD8+ T cells and antibody-secreting plasma cells, which are responsible for viral control and clearance in the later stages of infection. In coronavirus disease 2019 (COVID-19), gut barrier dysfunction and depletion of symbiotic microorganisms eliminate the aforementioned immunomodulatory effects and compromise the ability of the respiratory immune system to effectively contain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; B: The gut vascular bed has a massive endothelial surface that is susceptible to SARS-CoV-2 infection. SARS-CoV-2 can inflict direct injury to angiotensin-converting enzyme 2 (ACE2)-expressing endothelial cells; interruption of ACE2 signaling can dysregulate both the renin-angiotensin and kinin-kallikrein systems, leading to vascular leakage. The activated or apoptotic endothelial cells release phosphatidylserine-rich endothelial microparticles and secrete large amounts of tissue factor, VIIIa, von Willebrand factor, and other procoagulant cofactors. Circulating platelets accumulate at sites of vascular injury, adhere to each other, and become activated, leading to further secretion of prothrombotic substances. Overexpression of adhesion molecules, such as P-selectin, facilitates the recruitment and activation of monocytes and other leukocytes, including neutrophil extracellular trap (NET)-producing neutrophils. COVID-19-associated immunothrombosis refers to this concurrent aberrant activation of the innate immune and coagulation systems, which predisposes to serious thrombotic complications. This vicious cycle can be further exacerbated by gut barrier dysfunction. Low-grade endotoxemia, due to increased intestinal permeability, enhances the activation of endothelial cells and platelets by inducing lipopolysaccharide (LPS)/toll-like receptor 2 (TLR2) and LPS/TRL4 downstream signaling pathways. In parallel, LPS is a potent driver of NET formation. Several other bacterial lipoproteins, such as peptidoglycan-associated lipoprotein (Pal) or Pam^3Cys, aggravate vascular leakage and precipitate thrombus formation through TLR2 activation. Moreover, translocation of fungal components, such as β-glucan, could directly stimulate leukocytes and promote inflammation by binding to the Dectin-1 receptor and activating the nuclear factor-κB pathway. Finally, gut dysbiosis is associated with trimethylamine N-oxide overproduction, which is a recognized risk factor for clotting events as it enhances platelet hyperresponsiveness, endothelial dysfunction, and NLR family pyrin domain containing 3 inflammasome activation (created with biorender.com). AngII: Angiotensin II; DCs: Dendritic cells; ECs: Endothelial cells; NK cells: Natural killer cells; NO: Nitric oxide; PLT: Platelet; DAT: Desaminotyrosine; SCFAs: Short-chain fatty acids; PRRs: Pattern recognition receptors.

proliferation by driving the expression of IFN-α/β receptor[113]. In line with this, when mice were exposed to antibiotics, their macrophage-related type I and type II IFN responses were severely impaired, resulting in the uncontrolled spread of systemic lymphocytic choriomeningitis virus or mucosal (influenza virus) infection. In a murine model of influenza infection, desaminotyrosine (DAT), a degradation product of dietary flavonoids, induced an efficient amplification of the IFN type I loop, which suppressed viral gene expression and airway epithelial damage. Notably, a distinct human-

derived commensal, *Clostridium orbiscindens*, produced DAT and rescued antibiotically-treated mice from viral infection[119]. An outer membrane glycolipid originating from the gut symbiont *Bacteroides fragilis* protected mice against viral infection through the induction and systemic release of IFN-β by colonic DCs[120]. Acetate, another metabolite derived from the gut microbiome, is able to enter the circulation, enhance IFN-β signal transduction *via* stimulation of the G-protein-coupled receptor 43 in pulmonary epithelial cells, and thus limit severe RSV infection[114]. Moreover, depletion of commensal bacteria precipitated significant epigenetic modifications at the level of mononuclear phagocytes residing in non-mucosal lymphoid organs. As a result, these cells were unable to induce type I IFN secretion, which led to suboptimal NK cell priming and poor antiviral responses[121]. Admittedly, an imbalance of IFN signaling is an inherent characteristic of the pathogenesis of respiratory tract infections, including SARS-CoV-2-associated pneumonia[122]. Early severe COVID-19 is governed by overwhelming IFN-α responses as well as NK cell functional exhaustion, which is manifested by abnormal expression of interferon-stimulated genes[123]. Therefore, it is plausible to assume that metabolites and signals stemming from luminal bacteria could influence the early response to SARS-CoV-2 infection by altering the IFN signature and compromising innate immunocompetence in the lungs.

Regulation of the mucosal immune system of the respiratory tract, which supervises airway colonization, depends on reciprocal signaling with the gut. The respiratory tract is not sterile; instead, it harbors a unique microbial ecosystem and its role in homeostasis and disease is being increasingly recognized with the advent of culture-independent molecular techniques[124]. Alterations of the lung microbiome signature are associated with clinical outcomes in critically ill patients infected with SARS-CoV-2[125]. The immunomodulatory potential of airway bacteria was exemplified by a pathogen-free murine model of influenza virus. Colonization of the upper respiratory tract by *Staphylococcus aureus* induces the recruitment of peripheral macrophages into the alveoli and their polarization toward an M2-like phenotype *via* TLR2 signaling. As a result, *Staphylococcus aureus* creates an anti-inflammatory pulmonary milieu that attenuated immune-mediated injury and prevented lethal influenza infection [126].

The robust and timely priming of adaptive immunity is necessary to contain SAR-CoV-2 infection. Delayed activation of adaptive immune responses and depletion of virus-specific T cells are hallmarks of severe or fatal COVID-19[127]. Interestingly, multiple studies have revealed that the gut microbiome is actively involved in shaping adaptive immunity in the respiratory tract. In a murine model of West Nile virus infection, exposure to antibiotics impaired the ability to elicit potent T cell responses, decreased the number of virus-specific CD8+ T cells, and led to worse disease outcomes[118]. Ichinohe *et al*[115] demonstrated that intestinal microflora regulates an even broader spectrum of adaptive immunity responses in the respiratory mucosa. More specifically, neomycin-sensitive commensal bacteria were essential for the induction of effective humoral responses and the generation of virus-specific CD4+ and CD8+ T cells in the lungs. Normal intestinal flora provided signals that maintained a steady-state IL-1β, pro-IL-18, and NLR family pyrin domain containing 3 (NLRP3) expression. Antibiotic-induced immunodeficiency is attributed to impaired inflammasome activation, abnormal activation and distribution of respiratory DCs, and inadequate DC migration to draining lymph nodes of the lung[115]. In this setting, Gauguet *et al*[128] demonstrated that the presence of segmented filamentous bacteria in the murine microbiome was vital for priming strong Th17 immunity responses and IL-22 secretion in the respiratory system. In response to fiber supplementation, the gut microbiome generates large amounts of SCFAs, which hinders influenza-induced lung injury through a dual mechanism concerning both arms of immunity[129]. First, SCFAs enhances the cellular metabolism and the effector functions of CD8+ T cells in the respiratory tract. Second, SCFAs induce an alternative activation of macrophages, which exhibit the limited ability to express the chemokine CXCL1. As a result, SCFA-modulated macrophages reduce early neutrophil infiltration and subsequent injury in the airways[129]. In a randomized controlled trial, non-hospitalized patients with symptomatic COVID-19 were allocated 1:1 to groups receiving an oral probiotic formulation or placebo for 30 d. Remarkably, probiotic supplementation was associated with higher rates of complete remission, decreased nasopharyngeal viral levels, and shorter duration of symptoms by inducing vigorous virus-specific IgM and IgG antibody responses.

In summary, a well-preserved intestinal barrier function, harboring a diverse consortium of commensal bacteria, provides the essential signals for appropriate and effective modulation of immune system responses in the lungs. Regardless of being the cause or the result of severe SARS-CoV-2 infection, gut dysbiosis is not a silent bystander but an active orchestrator of dysregulated immune responses in the respiratory tract. Modulation of gut microbiota represents an emerging therapeutic intervention to mitigate immune-mediated lung injury and improve COVID-19 outcomes[130].

GUT BARRIER DYSFUNCTION INFLAMING COVID-19-ASSOCIATED COAGULOPATHY

COVID-19-associated coagulopathy (CAC) is a life-threatening condition that can lead to arterial thromboembolism (ATE), such as acute coronary syndrome and cerebrovascular accident, or venous

thromboembolism (VTE), which manifests as deep vein thrombosis or pulmonary embolism[131]. Mild thrombocytopenia, prolonged prothrombin time, and increased serum levels of fibrinogen, CRP, P-selectin, and d-dimers have all been linked to clotting events in COVID-19 patients; these deviations become more pronounced as the disease progresses[131,132]. A recent meta-analysis, comprised of more than 90000 patients, concluded that hospitalized COVID-19 patients have a significantly increased 90-d risk of VTE in comparison to hospitalized individuals with influenza virus (9.5% *vs* 5.3%), and that this peril persists even after the breakthrough of effective vaccines[133]. COVID-19-related thromboembolic events are major burdens of morbidity and mortality, and their incidence increases with disease severity, affecting up to one third of patients in ICUs[134-136]. The pathophysiology underlying CAC is multifactorial, encompassing endothelial injury, over-exuberant immune responses, and overt dysregulation of coagulation and fibrinolytic pathways, which collectively result in a procoagulant state[131]. The activation of these mechanisms can be further aggravated by defects in intestinal barrier integrity due to SARS-CoV-2 infection[27,137].

The dysfunction of the endothelium is a hallmark of COVID-19, representing a common feature in multiple clinical manifestations of the disease such as thromboembolic events, neurological complications, and renal dysfunction[138,139]. The intestinal tract accommodates an enormous vascular endothelial surface consisting of a monolayer of squamous endothelial cells. Under physiological conditions, endothelial cells regulate the vascular tone and secrete anticoagulant and antiplatelet agents that preclude clotting events[140]. Human endothelial cells express the key cofactors, namely ACE2 and TMPRSS2, which are exploited by SARS-CoV-2 to invade its target cells[141]. There is evidence of viral inclusions in endothelial cells and mononuclear cell infiltrates in the walls of small vessels, as well as markers of endothelial cell apoptosis[142]. SARS-CoV-2-induced dysfunction of gut microvasculature and fragmentation of the endothelial glycocalyx eliminate these protective effects, promote vasoconstriction due to depletion of endothelium-derived nitric oxide, and drive platelet activation and fibrin formation[131]. Indeed, mesenteric thrombosis is not uncommon in critically ill patients with COVID-19, while focal ischemic lesions, inflammation of the endothelium, vessel wall edema, microhemorrhage, and microthrombi are frequent findings in resected bowel segments[27,143-145]. SARS-CoV-2-mediated dysregulation of ACE2 signaling in intestinal vascular endothelium might create a prothrombotic microenvironment through a dual mechanism. First, ACE2 catalyzes the conversion of angiotensin (Ang II) to angiotensin 1-7 (Ang 1-7), which confers important antithrombotic and immunoregulatory effects by binding to G-protein coupled Mas receptors. Therefore, ACE2 depletion attenuates the Ang 1-7 downstream pathway and shifts the balance in favor of Ang II, which binds to its cognate receptor and exerts harmful prothrombotic and inflammatory effects[146]. Second, the kinin-kallikrein system is also directly modulated by ACE and ACE2. Thus, the ACE/ACE2 imbalance can induce a "kinin storm" and amplify vascular permeability, cell migration, platelet activation, and oxidative stress[131,147].

There are data supporting the hypothesis that SARS-CoV-2 inflicts damage on endothelial cells (endotheliitis) *via* both direct cytopathic and indirect immune-mediated mechanisms[148]. Activated or apoptotic intestinal endothelial cells retract their margins, release endothelial microparticles (MPs), and abolish their ability to confine phosphatidylserine (PS) into the inner layer of the cellular membrane[27,149]. In this setting, microRNA expression in endothelial-derived extracellular vesicles has been associated with cerebrovascular events in COVID-19 patients by compromising the function of the blood-brain barrier[150,151]. Endothelial MPs and PS-positive filopods support the formation of the prothrombinase complex along with activated coagulation factors Va and Xa and thereby catalyze a pivotal step of the coagulation cascade, that is, the proteolytic activation of thrombin[27,152]. In parallel, exposure of subendothelial tissues and tissue factor (TF) to plasma procoagulants triggers the extrinsic coagulation pathway[132]. Damaged endothelial cells sustain this hypercoagulable milieu and promote platelet aggregation by secreting large amounts of factor VIII and von Willebrand factor (VWF), respectively[153-156]. Thrombotic microangiopathy is further exacerbated due to relative deficiency in metalloproteinase ADAM metallopeptidase with thrombospondin type 1 motif 13 activity in COVID-19 patients, which leads to insufficient VWF cleavage and enhanced platelet-vessel wall interactions[157]. Numerous other endothelial dysfunction markers, such as circulating endothelial cells, soluble (s)E-selectin, soluble thrombomodulin, and soluble intercellular adhesion molecule 1 are significantly increased in COVID-19 patients receiving ICU care[153,155,158]. Furthermore, critically ill patients demonstrate functional exhaustion of natural anticoagulants (protein C, protein S, and antithrombin) and develop anti-phospholipid antibodies at high rates[154]. This procoagulant state is accompanied by suboptimal fibrinolytic potential and remodeling of the clot structure, which displays a denser fibrin network as well as thinner and shorter fibrin fibers. In severe COVID-19, hypofibrinolysis is dictated by an upregulation of plasminogen activator inhibitor-1 and its stabilizing cofactor vitronectin, which reduce plasminogen generation, despite concurrent elevations of tissue plasminogen activator[159].

Immunothrombosis illustrates the intricate cross-talk between the innate immune system and the coagulation pathway, which aims to locally contain an infection by facilitating recognition and eradication of invading pathogens. An aberrant activation of immunothrombosis is associated with severe thrombotic complications in SARS-CoV-2 infection[160]. Endothelium expresses a variety of adhesion and chemoattractant molecules, promoting the recruitment of monocytes and neutrophils at sites of injury. The release of DAMPs and PAMPs stimulates innate immune cells, which subsequently express TF and pro-inflammatory mediators in large amounts and precipitates the formation of

neutrophil extracellular traps (NETs)[156]. NETs are web-like structures consisting of DNA complexed with histones, bactericidal enzymes, complement factors, and coagulants. NETosis is a potent driver of immunothrombosis in COVID-19 and contributes to the procoagulant state in IBD through various mechanisms: cleavage of natural anticoagulants, direct activation of the contact-dependent and extrinsic pathways of coagulation, and aggregation of platelets[156,161]. In turn, activated platelets overexpress P-selectin and other adhesion molecules, which enhance their interactions with monocytes and NETs [162]. Through the secretion of their intracellular prothrombotic granule substances and externalization of their PS-rich membrane, platelets trigger and sustain thromboinflammation[131].

There is evidence that this vicious cycle could be further aggravated by gut barrier dysfunction. In particular, Oliva *et al*[163] reported that serum LPS and zonulin were increased in hospitalized COVID-19 patients and showed that endotoxemia was an independent predictor of in-hospital thrombotic complications. Zonulin is involved in the modulation of gut permeability by orchestrating the disassembly of intercellular TJ[53]. In this regard, serum LPS positively correlated with zonulin, supporting that low-grade endotoxemia precipitating thrombosis in COVID-19 originates from the gut [163]. In addition, thrombogenesis in patients with endotoxemia was associated with the TLR4-dependent activation of platelets[163]. In agreement, LPS/TLR4 and LPS/TLR2 downstream signaling pathways have been previously implicated in procoagulant conditions by promoting endothelial cell and platelet activation[164]. Several other bacterial lipoproteins, such as Pam^3Cys and peptidoglycan-associated lipoprotein, promote vascular leakage and thrombus formation through TLR2 activation [165]. In a murine model, microbial translocation and release of related patterns as a result of gut barrier leakage enhanced platelet pro-aggregating capacity and thrombus growth by inducing VWF synthesis; this effect was mediated *via* TLR2 activation in the hepatic endothelium[166]. Restoration of endothelial function through L-arginine supplementation was followed by improved outcomes in hospitalized patients with COVID-19[167]. L-arginine, a semi-essential amino acid, stimulates endothelium relaxation by serving as a substrate for the synthesis of nitric oxide by NOS. It also plays a role in immunomodulation by controlling T cell proliferation[168]. The importance of gut microbiome homeostasis in preventing immunothrombosis and inflammatory damage was evidenced in a model of acute mesenteric ischemia/reperfusion injury. More specifically, commensal bacteria mitigated LPS-induced NETosis by providing tonic stimulation of the neutrophil-intrinsic TLR4 downstream signaling [169]. Furthermore, perturbation of intestinal microflora due to SARS-CoV-2 infection and the ensuing depletion of SCFAs might enhance thromboinflammation by eliminating the inhibitory effects of butyrate on the LPS/TLR4/NF-κB pro-inflammatory pathway[170]. Alternatively, dysregulation of microorganisms involved in the metabolism of trimethylamine and its metabolite TMA N-oxide (TMAO) could contribute to the hypercoagulative state in CAC[171]. TMA is generated by gut bacterial metabolism of choline, carnitine, and betaine and is rapidly converted into TMAO in the liver. TMAO is a recognized risk factor for clotting events by enhancing platelet hyperresponsiveness, endothelial dysfunction, and NLRP3 inflammasome activation[171,172]. Indeed, a recent study revealed significant alterations in metabolites pertaining to the choline/TMAO and carnitine/TMAO pathways in COVID-19 patients; these aberrations were associated with disease symptoms and severity[173].

GUT BARRIER DYSFUNCTION: AN UNDERAPPRECIATED DRIVER OF SYSTEMIC INFLAMMATION

The critical form of COVID-19 is governed by multi-layered immune system dysregulation and hyper-inflammatory responses. Overexpression of pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and chemokines (MCP-1, MIP-1β, CCL5), as well as excessive oxidative stress and hyperactivation of the complement (C3a) and coagulation (d-dimer) systems are hallmarks of severe COVID-19[55,174]. In parallel, SARS-CoV-2 infection is accompanied by a tremendous influx of microbial components and metabolites into the systemic circulation due to intestinal barrier dysfunction. Several studies have shown that critically ill patients with COVID-19 present with endotoxemia and elevated plasma levels of zonulin and LPS-binding protein (LBP), which are surrogate markers of leaky gut[55,59,108,174-177]. Additional indices of disrupted intestinal permeability, such as fatty acid binding protein 2, an intracellular protein specifically expressed in IECs, and peptidoglycan, a core element of the cell wall in Gram-positive bacteria, were also increased in COVID-19 cases[178]. Furthermore, patients with severe COVID-19 as well as those with SARS-CoV-2 post-acute sequelae (PASC) had higher circulating levels of β-glucan, a fungal cell wall polysaccharide, indicating persistent fungal translocation[55,175,179]. Interestingly, the presence of circulating bacteriome in critically ill COVID-19 patients without evidence of secondary infections further corroborates the assumption of gut-derived bacterial translocation in severe SARS-CoV-2-infection[175]. Essentially, exuberant translocation precipitates microbial-mediated myeloid activation as demonstrated by increased serum levels of sCD14 and myeloperoxidase, which correspond to monocyte and neutrophil inflammation, respectively[55,174]. Multiple studies have revealed strong and unequivocal correlations between intestinal barrier dysfunction and biomarkers of inflammation and/or immunological activation, implicating a detrimental role of gut barrier defects in triggering or enhancing hyper-inflammatory responses in severe SARS-CoV-2 infection[55,59,108,163,

174,177]. More specifically, Giron *et al*[55] reported that LBP, β-glucan, and zonulin levels were all significantly associated with higher systemic levels of IL-6. During PASC, β-glucan could directly stimulate leukocytes and promote inflammation by binding to the Dectin-1 receptor and activating NF-κB pathway[179]. In hospitalized COVID-19 patients with cardiac involvement, NLRP3 inflammasome activation and subsequent IL-18 and IL-1Ra secretion were linked with circulating LBP levels[108]. In line with this, Sun *et al*[59] demonstrated that plasma levels of LBP were associated with inflammation biomarkers (CRP, IL-6, IL-8) as well as with changes in relative frequencies of lymphocytes and neutrophils. Endotoxemia was significantly associated with TNF-α, CCL5, and MIP-1β in another cohort of COVID-19 inpatients, whereas sCD14 was negatively associated with TGF-β[174].

Furthermore, gut microbiome alterations, which become more pronounced as disease progresses, showed solid correlations with markers of inflammation and tissue injury. In particular, gut dysbiosis coincided with derangements in the serum levels of IL-10, TNF-α, CRP, erythrocyte sedimentation rate, aspartate aminotransferase, and lactate dehydrogenase in patients with COVID-19[60]. A negative correlation was found between CRP and the symbiotic microorganisms *Faecalibacterium prausnitzii* and *Clostridium butyricum*, which perish in critically ill patients[60]. The abundance of commensal bacteria (*Lachnospiraceae*, *Eubacterium ventriosum*, *Faecalibacterium prausnitzii*) was followed by an increased number of CD4+ T cells, CD8+ T cells, and NK cells[69]. Conversely, opportunistic pathogens, which are commonly overrepresented in the COVID-19-related gut microbiome, such as *Bacteroides dorei* and *Akkermansia muciniphila*, were positively correlated with pro-inflammatory cytokines, including IL-1β, IL-6, and IL-8[69]. Accordingly, the predominance of the emerging pathogen, *Burkholderia contaminans*, was accompanied by T cell anergy and complement activation[59]. In parallel, the prevalence of pathogenic species in SARS-CoV-2-induced gut dysbiosis predisposes to bacteremia, leading to secondary microbial bloodstream infections, and thus, to an increased risk of serious complications[178, 180]. It should be noted that dysbiosis induces multifaceted derangements in microbial-mediated metabolic functions, including regulation of amino acid, lipid, and carbohydrate metabolism, that could further contribute to worsening outcomes. In fact, severe COVID-19 disease is characterized by a drastic shift in the composition of gut-modulated biologically active molecules that engage in inflammation signaling and immune system activation[55,59]. The long-lasting alteration of the microbial signature due to SARS-CoV-2, characterized by the predominance of pathogenic species and activation of pro-inflammatory pathways, perpetuates intestinal inflammation and could lead to long-term complications, such as tumorigenesis and colorectal cancer[60,181]. Systemic immune activation in COVID-19, which is at least partially fueled by leaky gut, has been linked to all of the severe manifestations of the disease, including cytokine storm syndrome, ARDS, renal failure, cardiovascular events, thromboembolic disease, and neurological manifestations[182]. The co-existence of intestinal barrier dysfunction in individuals with underlying diseases, such as obesity, diabetes, colorectal cancer, or immunosuppression, could exacerbate endotoxemia and the consequent immune system overactivation, predisposing to a more severe disease course[182,183].

CONCLUSION

Although the respiratory tract is the main target organ of SARS-CoV-2 infection, severe COVID-19 is considered a complex disorder affecting multiple systems. The development of GI-related symptoms, long-lasting fecal shedding of viral RNA, and identification of the virus in human intestinal tissues have brought to the spotlight the potential effects of the GI system in COVID-19 pathophysiology. The integrity of the intestinal barrier is a *sine qua non* for the accomplishment of the diverse digestive and immunomodulatory functions of the GI tract. In this setting, SARS-CoV-2 is capable of inducing deleterious effects on the gatekeepers of paracellular transport, *i.e.*, TJs, as well as on intestinal epithelial and endothelial cells through direct ACE2-dependent or indirect immune-mediated mechanisms, or both. Apart from dismantling the mechanical structures of the mucosa, COVID-19 is accompanied by profound alterations of the intestinal microflora at taxonomic and functional levels that are associated with disease severity and the host's immune system activation. Furthermore, SARS-CoV-2 hijacks innate immune responses, principally through interference with IFN signaling, and, thus, leads to inappropriate trafficking and activation of virus-specific T and B cells. In turn, this multi-layered disruption of the gut barrier can exacerbate the underlying immunopathology of COVID-19 or precipitate serious complications.

The gut and the lungs, albeit anatomically distinct, participate in a bi-directional immunological crosstalk through their respective microbes and immune cells. A well-tuned intestinal barrier harboring a diverse community of commensal microorganisms is pivotal in modulating lung immune responses and the lung microbiome. Therefore, gut dysbiosis impairs the ability to prime vigorous immune responses in the respiratory tract to effectively contain viral infections such as SARS-CoV-2. Moreover, the gut vascular bed provides an enormous endothelial surface susceptible to SARS-CoV-2-mediated injury. Disease-activated and apoptotic endothelial cells are potent drivers of neutrophil/monocyte recruitment, platelet aggregation, and coagulation activation. In parallel, dysbiosis, endotoxemia, and systemic hyperimmune reactions shape a procoagulant state within the gut microvasculature that

possibly contributes to extraintestinal thrombotic complications or ARDS pathogenesis, which are common manifestations of severe COVID-19. A compromised gut barrier allows an excessive influx of intraluminal microbiota into otherwise sterile extraintestinal compartments. This systemic dissemination of microbial constituents and metabolites contributes, to a certain extent, to immune system activation and hyper-inflammatory responses that govern the severe form of COVID-19. Preexisting comorbidities plagued with impaired intestinal permeability, such as obesity, diabetes, cirrhosis, and autoimmune disorders, might act synergistically with SARS-CoV-2 to further aggravate endotoxemia and endotoxin-mediated immune activation, predisposing to a more complicated disease course. Modulation of the gut barrier function emerges as a promising intervention to prevent or alleviate severe COVID-19 and related complications.

FOOTNOTES

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Abstract

The coronavirus disease 2019 (COVID-19) disease was first detected in December 2019 in Wuhan, China. This disease is currently one of the most important global health problems. The novel coronavirus COVID-19 is a respiratory illness, that has caused a deadly pandemic that is spreading rapidly around the world. It is not only a respiratory system virus that causes severe lung disease, but also a systemic disease agent that can affect all systems. People with COVID-19 disease usually have respiratory signs, however, the liver disorder is not an uncommon presentation. In addition, many studies around the world have revealed that the liver is injured to various degrees in patients with severe acute respiratory syndrome coronavirus 2 disease. This review mainly focuses on the impact of COVID-19 on Liver Injury at various ages.

Key Words: Liver injury; Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; Minireview

Core Tip: Studies have shown that neonates have rare evidence of liver damage, and in terms of age, they show the least amount of liver damage in the face of coronavirus disease 2019 (COVID-19) among affected people. Also, many studies reported different patterns of liver damage among children with COVID-19 much less than in adults, which is probably related to differences in their innate immune system and adaptation. The highest rate of liver damage is in adult patients and aspartate aminotransferase levels had the highest relevance with mortality compared to other indices reflecting liver injury.

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INTRODUCTION

Coronaviruses are a big family of viruses belonging to the realm Riboviria, order Nidovirales, family Coronaviridae and subfamily Coronavirinae. This virus contains an RNA genome and belongs to the Coronaviridae family[1,2]. This virus is spread in a wide spectrum of humans, other mammals, and avian species, also inducing acute respiratory infections[3]. Types of coronaviruses including HCoV-NL63, HCoV-HKU1, HCoV-229E, and HCoV-OC43 have been presented as mild virulent human viruses worldwide[4]. These viruses cause mild to severe acute respiratory illnesses in humans[3]. Coronavirus disease 2019 (COVID-19) was identified for the first time in December 2019, in Wuhan, located in the capital of Hubei Province in the People's Republic of China[1]. Coronavirus disease 2019 is an infectious illness that has caused a lethal pandemic that rapidly extends worldwide[5,6]. The signs of COVID-19 appear approximately 5.2 d after the disease and last for a minimum of 41 d and a maximum of 14 d until the end of life[4,7].

In the early stages of COVID-19, it has been found that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not only a respiratory system virus that generates severe lung disease but a systemic disease factor that can involve all systems[8,9]. Some extrapulmonary involvement of SARS-CoV-2 disease is in organs like the liver, heart, or kidneys[10]. Many studies throughout the world have demonstrated that the liver is injured to differing degrees in patients affected by SARS-CoV-2 disease[8,9].

The liver is a vital member that is mostly responsible for the storage of glycogen and regulation of blood glucose levels, protein synthesis, metabolism of toxic substances, and very other physiological processes[8,9]. Liver dysfunction has been reported in 54% of hospitalized patients affected by COVID-19 disease, most of which are more severe in COVID-19[11]. Liver injuries have been documented in patients affected by COVID-19, and commonly have mild increasing liver enzymes range from 14% to 53%[12]. Patients with severe disease, especially those hospitalized in ICU, have shown a higher increase in transaminase enzymes than patients with mild to moderate severity[13]. Furthermore, few studies investigated the dynamic change of liver function during the COVID-19 pandemic. Also, no study to date has documented the incidence of a simultaneous increase in liver transaminases and total bilirubin levels in COVID-19 patients[14].

The purpose of this review is to evaluate the effect of COVID-19 on liver injury in various ages.

DEFINITION OF LIVER INJURY

Patients who make severe acute liver injury in the absence of preexisting chronic liver disease, usually indicate noteworthy liver dysfunction marked with coagulopathy, which is described as an international normalized ratio ≥ 1.5 and is classically defined as acute liver failure (ALF) when any degree of hepatic encephalopathy (HE) is existing[15]. The ALF types include: (1) Hyperacute: < 7 d; (2) Acute: 7–28 d, and (3) Subacute: 28 d to 6 mo, depending on latency between the beginning of signs and development of encephalopathy and coagulopathy[16,17].

HOW DOES COVID-19 CAUSE LIVER INJURY?

Liver injury is seen in patients with COVID-19, and its harshness is altered depending on the patient's age, geographical area, and disease severity[18]. Viral direct damage[19], immune damage, systemic inflammatory response, drug-induced, ischemia-reperfusion injury, mechanical ventilation, and underlying diseases may donate to liver injury[20] (Figure 1).

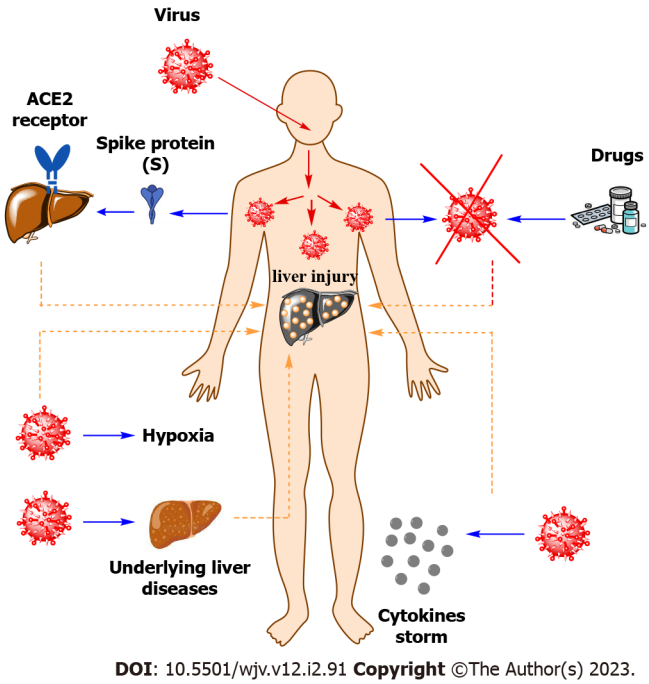

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Figure 1 Summary of liver injury in coronavirus disease 2019 patients. ACE2: Angiotensin-converting enzyme 2.

There is much evidence that COVID-19 causes abnormal liver function experiment outcomes with increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in people with liver damage[21,22]. Studies performed in Wuhan, China, recorded mildly elevated ALT and AST levels in 14%–53% of cases, with higher rates of both enzymes in patients with intense infection, mostly in patients requiring admission to the intensive care unit[23]. In COVID-19 patients with injured biliary tract were increased serum bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) levels[24]. Also, in cases where the virus causes notable liver injury and intense clinical symptoms, varying levels of ALP and GGT along with high levels of ALT and total bilirubin have been reported in 58%-78% of patients[25].

The pathophysiology of liver damage may include the cytopathic result, in which spike (S) protein of coronaviruses 2019 attaches to the angiotensin-converting enzyme 2 (ACE2) receptor, leading to reduced liver function and hepatobiliary disease[26]. S protein viral entry into the liver cells (hepatocytes and cholangiocytes), a process that involves binding to the surface of the host cell through binding of the surface unit (S1) to a receptor[27,28]. The virus attains access to the host *via* the ACE2 receptor (a type I integral membrane protein containing zinc, which indicates enzymatic action through cleaving the vasoconstrictor peptide angiotensin II to angiotensin I, a strong vasodilator peptide, therefore decreasing blood pressure). ACE2 receptor was abundantly demonstrated in epithelial cells that line a three-dimensional network of bile ducts named cholangiocytes (60%), hepatocytes (3%) in the liver, alveolar cells of the lungs, and in various organs such as the pancreas, kidney, and heart[29,30].

FACTORS RELATED TO THE COVID-19 DISEASE THAT CAUSE LIVER DAMAGE

Drugs: There are several drugs that prescribed to manage the treatment of patients with COVID-19 and associated symptoms, including therapeutic agents such as antivirals, antibiotics, acetaminophen, immunomodulators, corticosteroids, steroids, and antipyretics, that are metabolized through the liver and their use may lead to hepatotoxicity[31,32]. It has been reported that liver damage caused by these drugs is reason of anomalies in liver experiments and histological variation like micro-vesicular steatosis and liver inflammation in COVID-19 patients. Drugs like oseltamivir, arbidol, hydroxy-chloroquine, as well as ritonavir, and lopinavir in the treatment of patients may induce variable degrees of hepatotoxicity[33].

Hypoxia: Hypoxia in patients with COVID-19 is known as a major factor that causes a decrease in oxygen saturation values and finally reduction in systemic blood pressure[34]. This will ultimately cause a reduction in liver arterial perfusion *via* liver ischemia and hypoxia reperfusion injury *via* liver cell hypoxia[35].

Cytokines storm: Another factor related to COVID-19 that causes liver damage is the occurrence of a cytokine storm. In cases of the moderate and severe phase of the disease, which includes endothelial damage, it is related *via* a strong immune response to the SARS-CoV-2 virus[36]. This step is accompanied by the stimulation of inflammasomes (cytosolic multiprotein oligomers) that are responsible for the activation of caspase-1 and the release of pro-inflammatory cytokines [Interleukin (IL)-1β, IL-6, and IL-18][37]. In the next step, these cytokines stimulate the expression of genes relevant to the immune response, and through intracellular signaling, especially using IL-6, other pro-inflammatory cytokine biomarkers like tumor necrosis factor-alpha, IL-2, IL-8, IL-10, IL-17, granulocyte colony-stimulating factor monocyte chemoattractant protein, and interferon-inducible protein[38]. In addition, IL-6 activates numerous downstream signal pathways using creating complexes with its receptor[39], and also the reason for raised ferritin and C-reactive protein levels, reduced lymphocytes and enhanced neutrophils[40].

Underlying liver diseases: Underlying liver diseases can aggravate liver damage in the face of COVID-19. The prevalence of underlying liver diseases in patients with COVID-19 has been reported to be between 3% -11% in large observational studies[27,41,42]. From cases of these underlying diseases can be mentioned chronic liver disease and cirrhosis, non-alcoholic fatty liver disease, and liver transplantation[27].

THE ASSOCIATION DIFFERENT AGES AND LIVER INJURY CAUSED BY COVID-19

Many studies have demonstrated various patterns of disease and their outcomes between adults and children, possibly associated with the difference in their innate and adaptive immune systems. Children with or without chronic sickness are less likely to have a severe illness from COVID-19 confirmed in various studies[43]. However, children affected by COVID-19 have a milder infection than adults, possibly related to children having preserved effector and immunosuppressive components[44]. The differences in age, gender, and population are probably due to differences in immune responses and different variants of SARS-CoV-2[45]. Furthermore, children are less likely to have multiple chronic conditions than older people[44]. Children with a weakened immune system, such as liver illnesses considered at higher risk of coronavirus[43]. Some reports showed children to have higher ACE2 expression than older adults, that it conversion ang I (angiotensin I enzyme) into angiotensin 1-7 (ang 1-7) enzyme, thus ang 1-7 enzyme protecting against pulmonary capillary leak and inflammation. This issue can be the reason why children are more resistant to COVID-19 than adults. The mechanism of liver injury in cases by COVID- 19 is indistinct[46]. The liver damage associated with COVID-19 is described as any liver injury happening during the progression and treatment of this disease in cases with or without underlying liver illness[47]. The most common presentation of liver damage in patients is with COVID-19 shown by increasing liver enzymes and also decreasing Serum albumin in severe cases. However, reports of death in affected by COVID-19 patients due to severe liver injury rarely happen[48,49].

THE EFFECTS OF COVID-19 ON LIVER INJURY IN NEONATES

A clinical study of 10 neonates (including twins) to 9 born to mothers with COVID-19 showed that only two infants have thrombocytopenia accompanied using abnormal liver function[50]. Clinical Analysis of 48 Neonates Born to Mothers with COVID-19 (confirmed or clinically diagnosed) or without it accomplished by Liu *et al*[51] polymerase chain reaction (PCR) test of all neonates was negative. Evidence of vertical transmission and liver injury was not observed. Similarly, a clinical investigation of 19 neonates born to mothers with COVID-19 was investigated at Tongji Hospital, China. The COVID-19 real-time reverse-transcription–PCR Test of all neonates was negative. In this study also, vertical transfer of SARS-CoV-2 was not found[52]. Wang *et al*[53] investigated a case report of neonates with positive test results for coronavirus 36 h after birth. Nevertheless, whether this Newborn is vertical transfer from the mother to the neonate is yet to be verified. In this case, was observed a significant increase in AST and abnormalities in liver function tests. Stolfi *et al*[54] reported a neonate of vertical transmission of COVID-19 with liver injury, confirmed using an increase in serum transaminases in Italy. The positive PCR test of COVID-19 in a neonate less than 24 h after C-section probably indicates vertical transmission, therefore proposing a transplacental transfer of SARS-CoV-2. Liver damage in this neonate was created probably using a direct virus-mediated mechanism that correlated to ACE2 receptor expression, But the details are unknown. Out of 33 neonates born to mothers affected by COVID-19 in China, three cases have positive PCR tests for COVID-19. One neonate had observed increasing transaminases[55].

THE EFFECTS OF COVID-19 ON LIVER INJURY IN ADULTS

Guan *et al*[56] extracted information about 1099 patients with positive PCR tests for COVID-19 in 30 provinces in China (from 552 hospitals). Out of 1099 patients, 112 cases (with an average age of 47 years) had a slight increase of AST with mild illness, and 56 adults had a high increase of AST with severe illness. In 2020, in a national retrospective cohort study in France, Mallet *et al*[57] examined the danger of mortality after COVID-19 disease in adult with chronic liver disease. The study contained 259,110 of all adults with COVID-19 who were released from post-acute care and acute, public and private hospitals in France in 2020. From a total of 259,110 patients who were between 54 and 83 years old (average age 70 years) and 52% were men, including 10,006 (3.9%) and 15,746 (6.0%) patients with alcohol use disorders and chronic liver disease, respectively. The results of this study demonstrated that patients with uncompensated cirrhosis, primary liver cancer, and alcohol use disorders were at high risk for COVID-19 fatality, while patients with compensated cirrhosis, mild liver disease, organ, including liver transplant, or acquired depressive syndrome were not at risk of COVID-19 mortality. Overall, mortality was in 38,203 (15%) of the patients, including chronic liver disease 2,941 (19%) and 7,475 (28%) after mechanical ventilation.

In another study, Mantovani *et al*[42] evaluated the widespread outbreak of chronic liver disease among patients affected by COVID-19 with a meta-analysis of data in observational studies and investigating the association between the liver injury and COVID-19 disease. The number of 11 observational studies included 2034 adults aged between 45 and 54 years (average age of 49 years), and 57.2% were men. The results of this study revealed that the widespread outbreak of chronic liver disease was 3% and people with severe disease of COVID-19 had associated changes in liver enzymes and coagulation profiles, which were reported to be possibly due to an innate immune response to the virus. In addition, the findings of this study displayed that the gain in AST level in hospitalized severe patients was more frequent and significant than the gain in ALT, and AST levels had the highest relevance with mortality compared to other indices reflecting liver damage, and it was reported that common factors related with the increase in liver damage indicators were the enhance in the number of neutrophils, the decrease in the number of lymphocytes, and male gender. The association between liver damage and adverse events of Coronavirus disease is indistinct. In adult studies, a higher rate of liver enzymes was reported in adults with severe diseases than in milder diseases[43]. One of the limitations of this study is that it is a retrospective study, which may have inadvertently missed some studies with basic keyword searches. In addition, the mechanism of liver damage at COVID-19 patients with different ages in used studies has not been clarified. However, this study was summarized existing evidence on the effects of COVID-19 on the liver injury at various ages. Furthermore, this study might have helped in clinical diagnosis and treatment for COVID-19related liver disease.

Figure 2 shows a summary of the effects of COVID-19 on Liver Injury at various ages.

RECOMMENDATIONS AND FUTURE RESEARCHES

The mechanisms of liver damage in either adults or children with COVID-19 are not fully unclear and the impact of liver injury caused by new variants of COVID-19 in patients is unexplained. Furthermore, further investigation is required to determine liver involvement and the consequence of COVID-19 on various ages with liver disease. Also, the pathogenetic mechanisms of COVID-19 on liver injury of patients in different age groups need to be investigated.

CONCLUSION

Liver damage is seen in patients affected by COVID-19, and factors including viral direct damage, immune damage, systemic inflammatory response, drug-induced, ischemia-reperfusion injury, mechanical ventilation, and underlying diseases contribute to liver injury. The association between liver damage and adverse clinical outcomes in patients affected by COVID-19 and the mechanism of SARS-CoV-2 in creating this injury is also unclear. Studies have shown that neonates have rare evidence of liver damage, and in terms of age, they show the least amount of liver damage in the face of COVID-19 disease among affected people. Most patients with COVID-19 have maintained their normal liver function during the disease, but patients with more severe disease probably had an abnormal liver function. Also, many studies reported different patterns of liver damage among children with COVID-19 much less than in adults, which is probably related to differences in their innate immune system and adaptation. Most patients with COVID-19 have a mild increase in aspartate aminotransferase, alanine aminotransferase, or total bilirubin. The highest rate of liver damage is in adult patients and AST levels had the highest relevance with mortality compared to other indices reflecting liver injury.

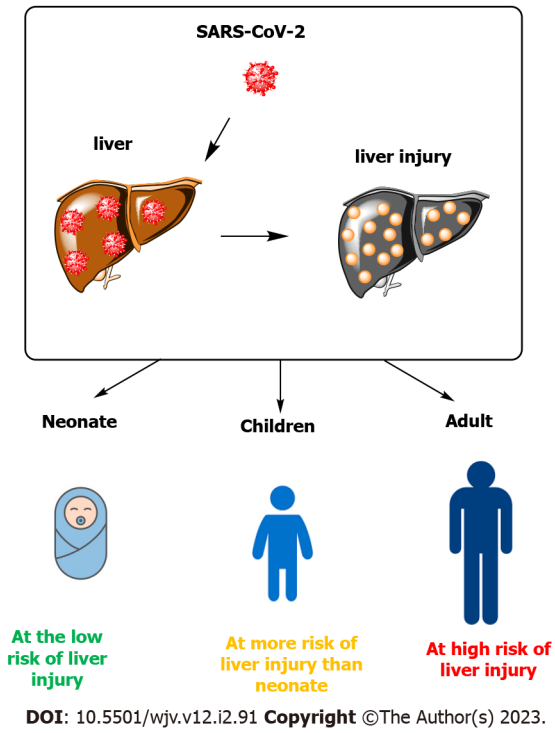

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Figure 2 Summary of liver injury of coronavirus disease 2019 according to the age of patients.

FOOTNOTES

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MINIREVIEWS

Immune-mediated liver injury following COVID-19 vaccination

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Abstract

Liver injury secondary to vaccination is a rare adverse event that has recently come under attention thanks to the continuous pharmacovigilance following the widespread implementation of coronavirus disease 2019 (COVID-19) vaccination protocols. All three most widely distributed severe acute respiratory syndrome coronavirus 2 vaccine formulations, *e.g.*, BNT162b2, mRNA-1273, and ChAdOx1-S, can induce liver injury that may involve immune-mediated pathways and result in autoimmune hepatitis-like presentation that may require therapeutic intervention in the form of corticosteroid administration. Various mechanisms have been proposed in an attempt to highlight immune checkpoint inhibition and thus establish causality with vaccination. The autoimmune features of such a reaction also prompt an in-depth investigation of the newly employed vaccine technologies. Novel vaccine delivery platforms, *e.g.*, mRNA-containing lipid nanoparticles and adenoviral vectors, contribute to the inflammatory background that leads to an exaggerated immune response, while patterns of molecular mimicry between the spike (S) protein and prominent liver antigens may account for the autoimmune presentation. Immune mediators triggered by vaccination or vaccine ingredients per se, including autoreactive antibodies, cytokines, and cytotoxic T-cell populations, may inflict hepatocellular damage through well-established pathways. We aim to review available data associated with immune-mediated liver injury associated with COVID-19 vaccination and elucidate potential mechanisms underlying its pathogenesis.

Key Words: Adverse effects; COVID-19 vaccines; mRNA vaccine; Autoimmune Hepatitis; Chemical and Drug Induced Liver Injury; Autoimmunity

Core Tip: Following the worldwide implementation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination protocols, several reports suggest an increase in the occurrence of autoimmune phenomena involving the liver. Studies on vaccine-induced liver injury point to a specific pattern of hepatocellular injury that involves immune-mediated pathways. This minireview explores the underlying pathophysiology of immune-mediated liver injury following SARS-CoV-2 vaccination and examines the most widely distributed vaccine formulations' autoimmune and hepatotoxic potential.

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INTRODUCTION

As of August 4, 2022, approximately 5.3 billion people around the world have received at least one dose of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine. Widespread implementation of vaccination protocols has successfully contained the spread of the pandemic and has reduced the disease burden for patients and health systems alike[1]. Newly employed vaccination platforms, *e.g.*, mRNA- and adenovirus (AdV)- based formulations, have achieved high efficacy rates combined with a good safety profile[2]. SARS-CoV-2 vaccines have undergone the most intensive safety monitoring in the history of mankind. Both active and passive monitoring systems have been employed in order to timely detect and properly identify adverse events related to vaccination[3,4]. This worldwide vigilance has proved fruitful for epidemiological purposes and has been instrumental in ensuring public support for vaccination. Most frequently reported adverse events have been mild in nature and local in character. They primarily concern injection site-related reactions, *e.g.*, topical pain and redness or generalized systemic symptoms, like fever and fatigue[5,6]. As far as serious, organ-specific adverse events are concerned, a very low risk of myocarditis mainly in younger individuals has been linked to vaccination with an mRNA vaccine, whereas adenoviral vector vaccines have been associated with incidents of thrombosis accompanied by thrombocytopenia and possibly Guillain–Barré Syndrome (GBS) cases. A rather rare side effect that has recently come under attention is that of liver injury following vaccination with a SARS-CoV-2 vaccine.

Drug-induced liver injury (DILI), under the umbrella of which such a clinical syndrome would initially be examined, is characterized by new-onset, profound increases in liver function enzyme levels. According to the latest expert panel update, this is defined as a ≥ 5 × upper limit of normal (ULN) elevation of alanine (ALT) or aspartate aminotransferase (AST) and/or ≥2× ULN increase in alkaline phosphatase (ALP) levels or ALT/AST ≥ 3 × UNL and bilirubin ≥ 2 × ULN[7]. Upon removal of the offending agent, most cases of DILI are usually self-contained; corticosteroids are sometimes added to the therapeutic regimen if autoimmune features are demonstrated. In fact, most of the reported cases' clinical and histological features closely resemble those encountered in autoimmune hepatitis (AIH)[8,9], steering the focus of the causality investigation onto the immune-mediated background of the reaction. However, it remains unclear whether the reported association of AIH with vaccination is coincidental, represents unique SARS-CoV-2-induced antigen-specific immune activation or is associated with transient drug-induced liver injury. In this study, we aim to review underlying mechanisms driving immune-mediated liver injury following COVID-19 vaccination and discuss potential implications

METHODS

We carried out broad searches of PubMed, Scopus, and Embase between 1 January 2021 and 1 September 2022 to identify literature describing immune-mediated liver injury or autoimmune hepatitis following COVID-19 vaccination. Relevant publications were identified based on the titles and abstracts. No restriction on the type of paper or language was set, even though the main focus was put on underlying mechanisms. Two reviewers independently screened all titles/abstracts and hand-searched references of retrieved articles. Data were assessed for their quality based on overall judgement and not aggregate scores. Disagreements were discussed and resolved and duplicates were removed.

VACCINE-INDUCED AUTOIMMUNITY

Throughout the vaccine rollout period, there have been reported cases of presumed AIH that were attributed to COVID-19 vaccination because they were observed shortly after either the first or second dose of the vaccine, with the initial case described as early as January 2021[10]. AIH is part of a diverse group of chronic inflammatory liver conditions that include primary biliary cholangitis and primary sclerosing cholangitis, and its complex pathophysiology involves underlying genetic predisposition and interactions with environmental triggers[11]. Viral infections, drug exposure, and vaccinations have been implicated in the pathogenesis of AIH[12]. AIH had fallen under the radar during the phase 3 clinical trials of all vaccines, and like every other rare adverse event, much debate has ensued over its association with the vaccination. New onset autoimmune reactions following vaccination have previously been described in the literature[13]. Both Hepatitis A and Hepatitis B vaccines have been linked to the development of AIH-like conditions[14]. Human papillomavirus, Hepatitis B, and Influenza vaccines have been held accountable for autoimmune reactions[15,16]. Molecular mimicry theory has been the platform upon which causality with vaccination has been determined[17]. It has been hypothesized that individuals with a genetic predisposition to autoimmunity undergo vaccination, and similarly to other environmental inputs, *e.g.*, smoking and nutrition, their immune tolerance becomes compromised. Reportedly, susceptible groups include those with systemic lupus erythematosus, GBS, multiple sclerosis, and narcolepsy. Concerning SARS-CoV-2 vaccination, immune-based phenomena such as GBS, IgA nephropathy, immune thrombotic thrombocytopenia, and myocarditis have been linked to both novel vaccine platforms, *i.e.*, mRNA- and AdV-based formulations[18].

VACCINE-INDUCED LIVER INJURY

As of early 2021, case reports of documented AIH following COVID-19 vaccination have begun to emerge[19-21]. We estimate that AIH related to COVID-19 is almost 1 in 14 million, even though we do acknowledge that many cases remain undocumented[19]. Data mostly deriving from comprehensive case-series reporting liver injury following vaccination with SARS-CoV-2 vaccines, point to the fact that most cases are in fact, immune-related, with 57% of all patients displaying both autoantibody presence and IgG hyperglobulinemia. They mostly affected elderly females, with most of the reports originating from European countries, followed by the United States[20]. The mean time of symptom onset is close to three weeks following the first vaccination, with some individuals presenting as early as 3 d after and others coming in as late as a month later, suggesting some heterogeneity in the underlying response mechanism. The mean duration between receiving the first or second vaccine dose and subsequent onset of liver injury was 17.3 (11.2–23.4) days and was mostly associated with mRNA vaccines, possibly to their stronger immunogenic potency[20]. The presence of underlying autoimmune diseases (*e.g*, Hashimoto thyroiditis, primary sclerosing cholangitis) is evident in approximately 25% of patients and could explain temporal and spatial differences in manifestations and prevalence, respectively, according to genetic predispositions[22]. Antinuclear antibody (ANA) was by far the most prevalent autoantibody, followed by spinal muscular atrophy and anti-myocardial antibody (AMA), resembling a type 1 AIH pattern. Biopsy findings were also consistent with AIH in most individuals. Around 1/3 of those who did not undergo the diagnostic procedures fit the clinical profile of AIH. Icteric manifestations, including jaundice, choluria, and pruritus, account for around 2/3 of all presentations. Outcomes were similar in all three vaccine products, *i.e.*, BNT162b2, mRNA-1273 and ChAdOx1 nCoV-19. Although recovery time varied greatly among study populations, the mean time for transaminase normalization was calculated at 46 d[21]. Corticosteroid treatment proved safe and effective for all those who were prescribed. No relapse was noted in the subgroup of patients whose immunosuppressant treatment was discontinued and remission was maintained in all those who spontaneously recovered.

CAUSALITY OR CASUALITY

Establishing causality is by definition, a difficult task, while the mechanism of action of such a reaction remains elusive. Several theories have been proposed in an attempt to link clinical manifestations of hepatocellular injury to patterns of immune mediation involving vaccine ingredients and products. Molecular mimicry-based reactivity and pro-inflammatory interactions involving the SARS-CoV-2 spike protein have been explored (Figure 1)[23]. The vaccine adjuvants have also come under scrutiny. The BNT162b2 and mRNA-1273 vaccines employ lipid nanoparticle (LNP) coated mRNA technology, whereas the ChAdOx1 nCoV-19 vaccine is deoxyribonucleic acid based and utilizes AdV vectors. Both AdV and mRNA vaccine platforms are newly licensed; hence, many rare *in vivo* interactions are to be explored and clarified. A deeper look into the active ingredients of the vaccines may provide us with a plausible mechanism. The mRNA itself has been carefully designed and tested as to its immunogenic properties[24,25]; however, prior to translation, it may still be recognized by cytosolic and endosomal toll-like receptors. The encoded S-spike protein elicits a strong immune reaction that involves the

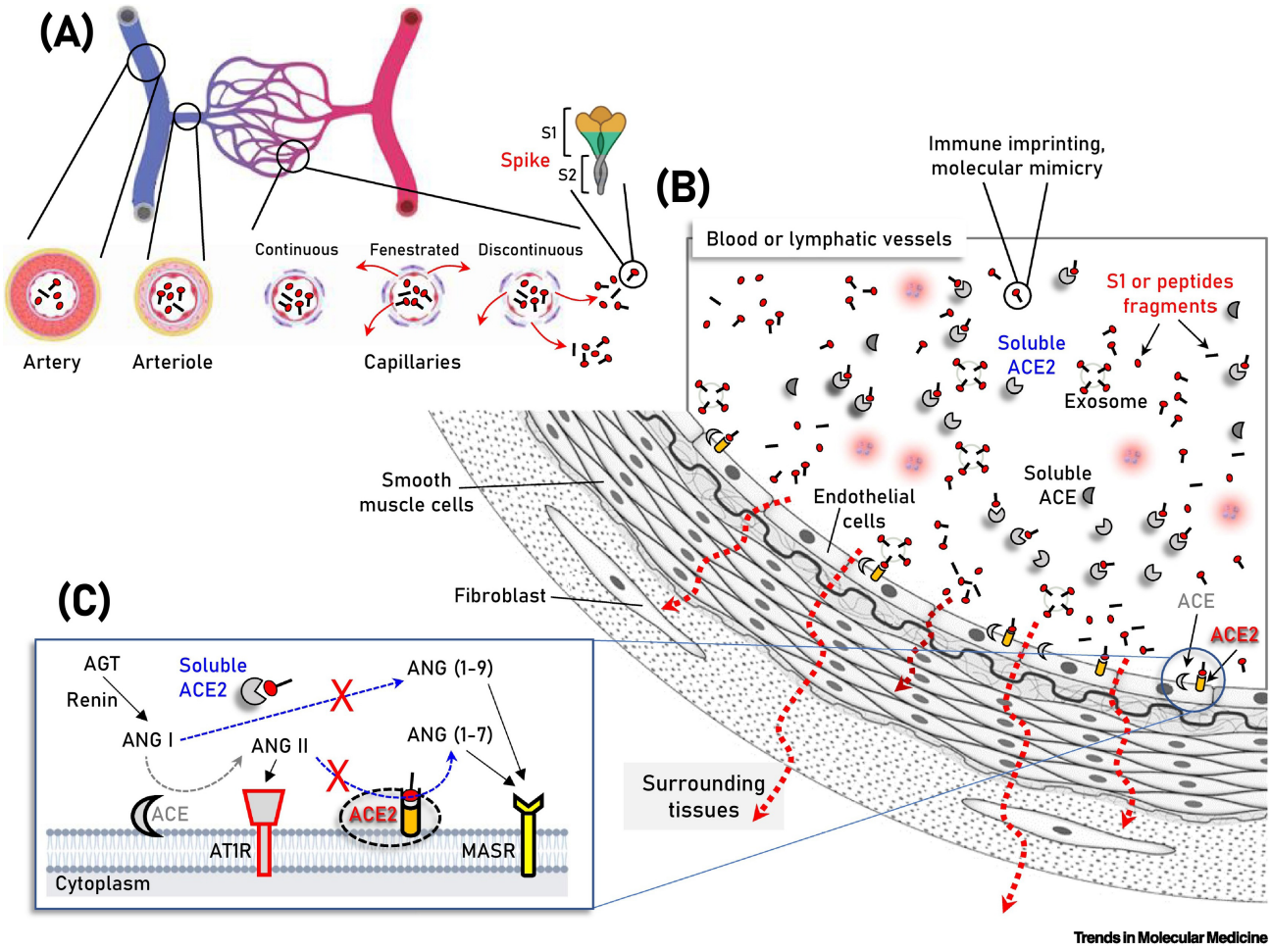

Figure 1 Schematic of the vasculature components showing vaccination-produced S protein/subunits/peptide fragments in the circulation, as well as soluble or endothelial cell membrane-attached angiotensin-converting enzyme 2. A: Parallel to immune system activation, circulating S protein/subunits/peptide fragments; B: Binding to angiotensin-converting enzyme 2 (ACE2) may occur not only to ACE2-expressing endothelial cells, but also in multiple cell types of the vasculature and surrounding tissues due to antigen diffusion (*e.g.*, in fenestrated or discontinuous capillary beds) (A, red arrows). These series of molecular events are unlikely for any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related antigen in the absence of severe coronavirus disease 2019, where SARS-CoV-2 is contained in the respiratory system; C: In the two counteracting pathways of the renin–angiotensin system (RAS), namely the 'conventional' arm, that involves ACE which generates angiotensin II (ANG II) from angiotensin I (ANG I), and the ACE2 arm which hydrolyzes ANG II to generate angiotensin (1–7) [ANG (1–7)] or ANG I to generate angiotensin (1–9) [ANG (1–9)] are depicted. ANG II binding and activation of the ANG II type 1 receptor (AT1R) promotes inflammation, fibrotic remodeling, and vasoconstriction, whereas the ANG (1–7) and ANG (1–9) peptides binding to MAS receptor (MASR) activate antifibrotic, anti-inflammatory pathways and vasodilation. Additional modules of the RAS (*i.e.*, renin and angiotensinogen, AGT) are also shown. AT1R: Angiotensin II type 1 receptor. Citation: Trougakos IP, Terpos E, Alexopoulos H, Politou M, Paraskevis D, Scorilas A, Kastritis E, Andreakos E, Dimopoulos MA. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. *Trends Mol Med* 2022; 28: 542-554. Copyright ©The Author(s) 2022. Published by Elsevier.

activation of the innate inflammatory cascade, as well as that of the adaptive humoral response. Regarding the former, SARS-CoV-2 vaccines employ the type I interferon pathway in particular, in order to maintain an adequate and effective immune response, that in turn, may increase the probability of an autoimmune occurrence in certain individuals[26]. Concerning the latter, reactivity between anti-S protein antibodies and human tissue antigens has been confirmed by a recent report[27]. The systemic distribution of the spike protein has also been postulated as a mechanism to explain adverse events by mRNA-based vaccines as well. Its interaction with soluble Angiotensin-converting enzyme 2 (ACE-2) and ACE-2-ligands may point to an organ-specific pattern of insult[28]. The presentation and/or production of the spike protein by the hepatocytes may induce the activation of cytotoxic T-cell subsets. Under this scope, the formation of immune complexes cannot be excluded. Their subsequent deposition on the liver may cause inflammation or exacerbation of the underlying autoimmune disease. Matyushkina *et al*[27] have identified the susceptibility of human leukocyte antigen (HLA) B15:01 and HLA B39:01 allele carriers to autoimmunity following COVID-19. HLA B15 has been strongly associated with the development of infliximab-induced liver injury[29], while HLA B39 has been recorded as one of the most prevalent alleles in AIH patients in Pakistan[30]. In the same report, although most autoreactive antibodies were associated with nuclear products, cross-reactivity with cytokeratin 18 (CK18), a prominent liver disease biomarker, was noted. Elevated anti-CK18 antibody titers have been described in AIH patients[31], and their relationship to the soluble liver antigen (SLA) has been established in the

literature. CK18's immunoreactivity has even been proposed but disproved as a potential diagnostic marker for the SLA subgroup of AIH patients[32]. The presence of SLA antibodies has been reported twice following vaccination with the mRNA-1273 vaccine, a fact that prompted investigators to conduct a genomic sequence analysis study which revealed, however, no homology between the SARS-CoV-2 spike protein and soluble liver antigen[33].

As far as AdV vectors are concerned, their clinical application as potential gene therapy delivery particles has been hindered by their hepatotoxic properties since the start of the century[34]. Recent reports have attributed this to their inherent liver tropism[34]. It should also be noted that the recombinant ChAdOx1-S AdV used in Vaxzervria formulations is likely hepatotropic since it is derived from a subset of non-human, Y25-coded adenoviruses that have been linked to viral hepatitis outbreaks in chimpanzees in the past[34]. In the same report, the authors build a case for a post-transcriptional modification taking place inside the nucleus of AdV-transduced host cells, resulting in alternate gene splicing and subsequent truncation of produced S-protein proteins that may in turn, be released in circulation. In addition to that, they demonstrated that in ChAdOx1-S-transduced hepatocytes, the truncated S-protein is the main splicing product, thereby providing us with another plausible mechanism to explain liver injury by AdV-based formulations. Of note, the spike protein produced by Vaxzervria has comparable receptor binding selection and affinity to its original counterpart[35]. Regarding common vaccine adjuvants, CpG 1018 and Aluminum, although widely used for immune response enhancement purposes and deemed safe by clinical trials[36] and regulatory authorities alike, have the potential to induce liver injury[37] and likely precipitate the development of auto-immune disease in a small percentage of the population[38]. Reportedly, none of the vaccines discussed in this review contain the aforementioned adjuvants, but future formulations may include them. Furthermore, we need to consider other vaccine formulation specificities, like the active ingredient's delivery system. The immunogenicity of the mRNA-containing LNPs has recently come under question, despite the fact that prior to their use in COVID-19 vaccines, they were being hailed as a potential genetic treatment platform for inherited liver disease[39]. The mRNA delivery particles have been linked to the development of allergic reactions[40], suggesting a plausible, if not definite, role as immune mediators. The LNP platform mounts a strong immune response, which relies on the medium's pro-inflammatory properties for its efficacy. Such an immune response-provoking environment could potentiate a loss in self-tolerance. LNPs have been known to act as adjuvants to vaccine-induced immune reactions[41,42]. In particular, LNPs seem to trigger the NLRP3 inflammasome pathway that has been implicated in the pathogenesis of other autoimmune phenomena, like pericarditis, rheumatoid arthritis and AIH[43-46]. The intense immunogenic character of LNPs has been demonstrated both histochemically and graphically in animal models through multiple route administration of its purified form, *e.g.*, intramuscularly and intranasally.

The hepatocellular type of injury that is predominantly associated with post-vaccination liver injury can also be attributed to the direct action of cytotoxic T-lymphocytes, as rapid and sustained activation of this cell subset has been confirmed in the context of SARS-CoV-2 vaccination[47]. In a recent report, vaccination with the BNT162b2 vaccine resulted in a CD8+ rich lymphocytic infiltrate in the liver of a patient that presented with probable AIH. The clonal expansion and peripheral activation state of this particular subset of lymphocytes correlated closely with the clinical course of hepatitis in this individual, suggesting T-cells' involvement in the development and resolution of the disease[48]. It has also been demonstrated, in animal models, that cytokine-activated, "bystander" CD8+ lymphocytes may cause hepatocellular injury even in the absence of a direct antigen[49]. Accumulation of cytotoxic infiltrates in the liver has been reported in the literature following acute infection in influenza pneumonia[50]. All the plausible mechanisms resulting in immune-mediated liver injury discussed above are presented concisely in Table 1.

DIAGNOSIS

The immune-mediated mechanism of a clinical syndrome involving hepatocellular injury would most likely be highlighted by an elevation in ANA and/or AMA titers in a similar fashion to AIH. A report from early on in the pandemic noted the presence of elevated autoimmunity markers, including ANA and AMA, in SARS-CoV-2 antibody-rich plasma, thereby suggesting their self-reactive potential[51]. However, otherwise typical AIH auto-antibodies may be present in the acute phase of liver injury by multiple causes[52]. In order to distinguish between them, a biopsy is the preferred option, with fibrosis being the prime differentiating factor[53]. Features of widespread fibrosis would be evident in an AIH-stricken liver[54], whereas evidence of acute or chronic inflammation with eosinophilic infiltration between or within the portal triads is to be expected in the case of direct liver toxicity, *i.e.*, DILI[55]. It is important to note that centrilobular necrosis is not a pathognomonic clue and should not be interpreted as such[56]. All in all, a definitive diagnosis of AIH may be challenging to make, as it relies on a constellation of clinical, serological and histological findings. Response to treatment with immunosuppressants is the only way to confirm a diagnosis[57]. AIH is a chronic condition with a high relapse rate if immunosuppression is withdrawn, whereas causes closely resembling AIH do not usually relapse[58].

Table 1 Immune-mediated phenomena concerning the liver, following severe acute respiratory syndrome coronavirus 2 vaccination

Mechanism of injury	Liver antigens	Immune mediators
Molecular mimicry	SLA	Autoreactive antibodies
	CK-18	
Cytotoxicity/Humoral response	S protein (membrane expression)	Activated CD8 + clone/protective anti-S antibodies
Humoral response	ACE-2 transmembrane receptor	Protective anti-S antibodies
Immune complex deposition	S protein (soluble)	
	Soluble ACE-2/ACE-2 ligand + S protein	
"Bystander" toxicity		Activated CD8 + clone
Loss of self-tolerance/Fibrosis		Type I IFN
NLRP3 inflammasome activation		LNPs
TLR-mediated innate immune response		mRNA

SLA: Soluble Liver Antigen; CK-18: Cytokeratin 18; S protein: Spike protein; anti-S: Anti-Spike protein; ACE-2: Angiotensin Converting Enzyme-2; IFN: Interferon; LNPs: Lipid nanoparticles; NLRP3: NLR family Pyrin domain containing 3; TLR: Toll-like receptor.

CONCLUSION

Immune-mediated liver injury remains an elusive but rare entity following COVID-19 vaccination. It is the responsibility of investigators and scientists worldwide to maintain a vigilant eye and continue reporting rare incidents related to vaccination with a high index of suspicion. However, adverse events as such, are significantly less frequent than potentially serious complications of COVID-19 disease[59] and should by no means discourage vaccination programs worldwide.

FOOTNOTES

Author contributions: Akinosoglou K and Gogos C conceived the idea; Schinas G performed the literature search, reviewed data, and wrote the manuscript; Polyzou E, Dimakopoulou V, and Tsoupra S performed the literature search and reviewed data; Akinosoglou K and Gogos C critically corrected the manuscript; Akinosoglou K revised the manuscript

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Abstract

There have been numerous concerns about the disease and how it affects the human body since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began in December 2019. The impact of SARS-CoV-2 on the

liver is being carefully investigated due to an increase in individuals with hepatitis and other liver illnesses, such as alcoholic liver disease. Additionally, the liver is involved in the metabolism of numerous drugs used to treat comorbidities and coronavirus disease 2019 (COVID-19). Determining how SARS-CoV-2 affects the liver and what factors place individuals with COVID-19 at a higher risk of developing liver problems are the two main objectives of this study. This evaluation of the literature included research from three major scientific databases. To provide an update on the current impact of COVID-19 on the liver, data was collected and relevant information was incorporated into the review. With more knowledge about the effect of the disease on the liver, better management and therapeutics can be developed, and education can ultimately save lives and reduce the long-term impact of the pandemic on our population.

Key Words: Coronavirus; COVID-19; SARS-CoV-2; Liver; Hepatic complications

Core Tip: We investigated the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the liver due to an increase in individuals with hepatitis and other liver illnesses, such as alcoholic liver disease. Additionally, the liver is involved in the metabolism of numerous drugs used to treat comorbidities and coronavirus disease 2019 (COVID-19). Determining how SARS-CoV-2 affects the liver and what factors place individuals with COVID-19 at higher risk of developing hepatic issues are the two main objectives of this study.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly infectious pathogenic coronavirus that appeared in late 2019 causing a pandemic of acute respiratory disease, which is known today as coronavirus disease 2019 (COVID-19)[1]. At a fast rate, the virus spread worldwide, replicated, and mutated into multiple major variants, posing a threat to global public health. SARS-CoV-2 is part of the order *Nidovirales*, family *Coronaviridae*, subfamily *Orthocoronavirinae, Betacoronavirus* genus, and *Sarbecovirus* subgenus[1,2]. It is a single-stranded, positive-sense, enveloped ribonucleic acid (RNA) virus that is 79.6% identical to SARS-CoV-2 and 96.2% like a bat-derived coronavirus strain[2]. The host receptor for SARS-CoV-2 cell entry is identical to SARS-CoV-2, the angiotensin-converting enzyme 2 (ACE-2)[3]. SARS-CoV-2 binds to ACE-2 with a higher affinity to the receptor-binding domain (RBD) of its spike protein[3]. Therefore, SARS-CoV-2 is more infectious**.** Since the first reports, which were discovered in Wuhan, China's Hubei Province, at the end of 2019, cases have been documented on every continent[3]. Globally, more than 500 million confirmed cases of COVID-19 from exposure to SARS-CoV-2 have been reported[3]. SARS-CoV-2 tends to replicate in the upper and lower respiratory tract and is transmitted by droplets and aerosols from asymptomatic and symptomatic infected subjects[4]. Most infections occur between 2-14 d (about 2 wk) with an incubation period of 5-7 d[4]. These infections tend to be uncomplicated. A small percentage of patients are hospitalized due to severe inflammation and pneumonia. Complications tend to be respiratory and multiorgan failure[4]. Risk factors for complicated diseases are older age, diabetes, hypertension, chronic cardiovascular disease, chronic pulmonary disease, and immunodeficiency[4]. The distribution of COVID-19 cases across most countries is highest in the age group of 20-59 years old[4]. Major reductions in social interactions have been implemented in many countries with SARS-CoV-2 outbreaks, leading to rapid reductions. An estimate of the infection fatality rate that is currently reported is 0.5%-1.0%[4]. Despite a rapid worldwide spread, attack rates have been lowered in most regions, demonstrating the efficacy of control measures[4].

Based on initial COVID-19 data, both healthy individuals and those with pre-existing liver disease infected with the SARS-CoV-2 virus exhibit abnormal liver function tests (LFTs), implying that the virus may play a direct role in liver damage[5]. The incidence of liver injury in patients with COVID-19 has been estimated to range from 14.8% to 53.0%[6]. A clinical study showed that patients with stable liver cirrhosis who contracted the SARS-CoV-2 virus can experience rapid deterioration as evidenced by an

increase in the Child-Pugh score[6]. The incidence of liver injury in cases of death from COVID-19 is 58.0%[6]. Liver injury following the contraction of the SARS-CoV-2 virus is characterized by hypoalbuminemia, hyperbilirubinemia, and an increase in alanine transaminase (ALT) and aspartate transaminase (AST)[5,6]. There may also be an increase in gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP), indicating injury to liver bile duct cells[6]. The degree of liver injury has a positive correlation with the severity of the infection. Mortality is statistically correlated with elevated AST and low albumin levels of 26.3-30.9 g/L[6]. The mechanism by which SARS-CoV-2 damages hepatocytes is still unclear; however, pathogenic mechanisms may include direct damage, immune-mediated, ischemia and hypoxia, thrombosis, and drug-induced[5,6]. This article aims to investigate the effects of SARS-CoV-2 on the liver and the risk factors for liver problems in coronavirus-infected patients.

METHODOLOGY

PubMed, Google Scholar, and Med Line Plus were used to conduct an electronic literature review. For the data compiled, the search was limited to peer-reviewed articles published between January 1, 2015, and July 1, 2022. The articles were chosen based on keywords such as coronavirus, COVID-19, SARS-CoV-2, and the effects of the virus on the liver. The articles were then examined and included depending on the topic's applicability.

REPORTED SYMPTOMS OF SARS-CoV-2 LIVER INJURY

Elevated LFTs in COVID-19

Altered LFTs have been observed in almost half of the hospitalized patients with COVID-19 infection [7]. In particular, elevated levels of liver enzymes glutamic-pyruvic transaminase (ALT), glutamic-oxaloacetic transaminase (AST), glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), and bilirubin have been seen to manifest as liver injury in such patients[6,8]. Previous studies have shown that the incidence of COVID-19 liver damage with elevated ALT ranges between 9.6% and 37.6%, elevated AST between 14.8 and 36.0%, and the proportion of abnormal GGT between 13.0%-24.4%[9]. These abnormal tests are the result of increased AST and ALT, whereas AST was more common than ALT. In addition, 10.5% to 69.0% of hospitalized COVID-19 patients showed abnormal LFTs. Hypoalbuminemia has also been reported as a consequence of COVID-19-related liver injury and was observed more significantly in men with COVID-19 compared to women[10]. When comparing and analyzing those with severe and non-severe COVID-19 cases, liver function abnormalities like hypoalbuminemia, GGT, aminotransferase, and bilirubin elevations were more frequent in those with severe disease as opposed to mild/moderate forms of the infection[11]. The liver injury caused by COVID-19 was related to the degree of severity of the infection and manifested as different degrees of liver function abnormalities[12].

Pathological changes in liver biopsies

Histopathological findings from liver biopsies of COVID-19 patients showed moderate microvascular steatosis with lobular and portal vein involvement[13]. Hepatocyte degeneration, with neutrophil infiltration of the hepatic lobes and sinusoidal enlargement of the central lobule, was observed. Congestion of hepatic sinuses with micro thrombosis and sinusoidal expansion, lymphocytic infiltration of the lobes, and hepatic necrosis in the periportal and centrilobular segments was also identified in patients [14]. Furthermore, pathological findings showed hepatocellular necrosis, cellular infiltration, an increase in the number of mitotic hepatocytes, and fatty degeneration[15]. In addition, COVID-19 Liver injury showed an elevation of eosinophilic bodies along with dilated hepatocytes[6]. Sinusothelial micro thrombosis disease was evident in approximately 20.0% of cases with focal endothelial damage[16]. Acinar atrophy was depicted in autopsy specimens in the late course of the infection[17]. Increased liver stiffness is also correlated with increased levels of biomarkers of liver injury, such as ALT and GGT, suggesting underlying hepatocellular and cholangiocellular damage at the biochemical level[18]. Changes in liver elasticity, viscosity, and steatosis levels were also observed in liver tissues in COVID-19 patients, with increased fibrosis compared to the control group ($P < 0.001$)[18]. In some studies, the liver appeared pale and yellowish on sectioning, with a nutmeg appearance[19]. The infection has been studied to cause cholangiocellular injury and cholestasis and consequently bile duct proliferation, with bile plug formation. In general, analyses have revealed that as the severity of COVID-19 in a patient increase, the levels of AST, ALT, total bilirubin, GGT, and ALP increase, resulting in a greater degree of liver injury, as observed in hepatocytes[20].

SARS-CoV-2 RELATED LIVER INJURY: PATHOGENIC MECHANISMS

Liver injury in patients infected with SARS-CoV-2 occurs *via* several mechanisms[21]. Several studies indicate that liver injury in patients with SARS has manifested through the elevation of liver enzymes, mainly ALT and/or AST in the early stage of the infection[21]. The incidence of liver injury in SARS patients ranges from 14.8% to 53.0%[21]. One hypothesis for the cause of liver injury is a direct invasion of the hepatic parenchyma by SARS-CoV-2[21]. Autopsy of patients with SARS found a large number of virus particles in the parenchyma and vascular endothelium of the liver[21]. The main receptor used by SARS to enter cells is ACE-2 which is abundantly present in cholangiocytes, endothelial cells, and the progenitor cells of the liver[22]. This results in acute liver and hepatitis biopsies in postmortem patients showing a significant increase in macrovesicular steatosis with eosinophilic bodies and high levels of mitotic cells suggesting hepatocyte apoptosis[21]. The results suggest that SARS infection causes direct injury to the hepatic parenchyma and concomitantly compromises the regenerative capability of the liver[22]. Hepatic injury is further exacerbated by the body's immune response to severe COVID-19 infection[23]. SARS activates both the innate and acquired immune system resulting in the release of high levels of several inflammatory cytokines by immune cells[23]. The resulting cytokine storm in severe SARS infections is the cause of death in 28.0% of fatal cases of COVID[24]. Multiorgan failure is a sequela of the cytokine storm, and the liver is no exception. Critically ill patients exhibited increased levels of interferon-lambda (IFN- λ), transforming growth factor-alpha (TGF-α), thymic stromal lymphopoietin, interleukin-16 (IL-16), IL-23, IL-33, and markers linked to coagulopathy, such as thrombopoietin. Patients with severe COVID are commonly anoxic due to respiratory failure. This requires patients to be mechanically ventilated and/or on vasopressor support. Lower cardiac output has a detrimental impact on the hemodynamics of the liver[23]. The resultant reduced hepatic blood flow can lead to anoxic hypoxic hepatitis and/or cholestasis[24]. Another complication of hepatic injury due to the high levels of inflammatory cytokines released by the body includes thrombosis and vascular congestion of the liver, which have been observed in autopsy samples of patients with severe COVID-19. Patients with severe COVID-19 were found to have elevated levels of total bilirubin and ALT, as well as elevated levels of inflammatory biomarkers such as IL-6, IL-10, C-reactive protein (CRP), and D-dimer. One of the mechanisms contributing to the damage observed in the liver of these patients is due to the SARS-CoV-2 infected cells which upregulate and produce large amounts of cytokines to help combat the virus, resulting in collateral damage to both infected and uninfected cells. This hyper-stimulated systemic inflammatory response induces macro- and micro-circulatory dysfunction, leading to global hypo-perfusion resulting in hypoxia, hypo-tension, and a hypercoagulable state. Therefore, microvascular thrombosis should be considered an important cause of liver injury and dysfunction in patients with COVID-19[25]. Hepatic injury during COVID-19 infection can be exacerbated by medications leading to elevated levels of ALT and AST. Remdesivir has shown *in vitro* antiviral activity against SARS-CoV-2 and a shorter recovery time in clinical trials, but elevated hepatic enzymes have also been reported as a major adverse drug reaction. Although some studies attribute this abnormal increase to viral infection rather than the side effect of the drug, others proposed that, whether or not it was affected by SARS-CoV-2, remdesivir increased the risk of hepatotoxicity. Other commonly used drugs to treat COVID-19 such as lopinavir/ritonavir have also resulted in hepatic injury. ACE medications and angiotensin II receptor blockers, which take a more focused approach, have also been reported to raise liver enzymes in COVID-19 patients. In autopsies of COVID-19 deaths, moderate microvesicular steatosis and mild lobular and portal activity were observed and probably associated with drug-induced liver injury. Other medications used for patients with COVID-19 that can trigger liver injury include antibiotics such as macrolides and quinolones, antivirals such as ribavirin, and even steroids[26].

SARS-CoV-2 INFECTION AND PRE-EXISTING LIVER DISEASES

The effect of COVID-19 on pre-existing liver diseases discussed below are hepatitis B and C virus infection, liver cirrhosis, liver cancer, liver transplant, non-alcoholic fatty liver disease (NAFLD), and alcoholic liver disease (Figure 1).

COVID-19 effect on hepatitis B virus and hepatitis C virus infection

Hepatitis C virus (HCV) and hepatitis B virus (HBV) were reported as the leading causes of liver diseases, but no specific data on the prevalence of these infections were provided. Many studies involving patients with COVID-19 showed a relatively low prevalence of chronic liver disease (CLD) at baseline, equal to 3.0%. Similarly, a prevalence rate of 3.0% CLD is associated with documented underlying chronic HBV or HCV infections in specific populations[27]. In one study of patients admitted to hospitals for COVID-19 in the northeastern United States, HCV infection was observed in $P < 0.1\%$ of patients, but information on HCV RNA levels was insufficient. In the same study, 23 cases (3.8%) presented positive HCV serology, of whom six patients (0.99%) had detectable viral HCV load at the time of hospital admission for the diagnosis of COVID-19[27]. In contrast, 2.0% of all patients

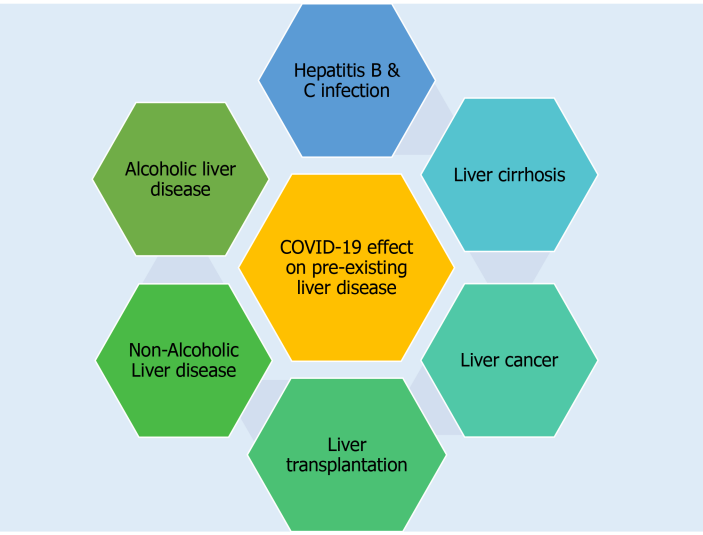

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Figure 1 Effect of coronavirus disease 2019 and preexisting liver disease.

showed hepatitis B surface antigen (HBsAg) positive chronic infection[27]. The study showed patients with recorded chronic HBV or HCV infection did not experience a more severe clinical course of COVID-19 compared to patients with HBsAg negative or undetectable HCV RNA, which measured the delay in SARS-CoV-2 clearance in HBV patients. Similarly, median viral clearance was not affected by preexisting HBV or HCV infection[27]. Lastly, chronic HBV or HCV infection (in the absence of cirrhosis) did not affect the prognosis of COVID-19 in the United States population.

COVID-19 effect on liver cirrhosis

Liver cirrhosis (Figure 2) increases the mortality of SARS-CoV-2 viral infection[28]. The pathophysiological mechanism for the SARS-CoV-2 virus begins with the spike glycoprotein (S) to allow viral entry into the target cell. The virus replicates to infect other surrounding cells through the ACE-2 receptor in cholangiocytes and hepatocytes to cause biliary and liver symptoms. Elevated liver enzymes are multifactorial and strongly associated with liver injury. A prevalent hepatic phenomenon associated with SARS-CoV-2 infection presents with elevated ALT and AST levels, with abnormal ALP and bilirubin readings[29]. Elevated serum levels of GGT, a marker of hepatobiliary cell injury, are found in a quarter of patients hospitalized with COVID-19[28]. Higher levels of a hepatocellular enzyme associated with severe cases of COVID-19 directly affect mechanisms that include increased cytokine release in the viral presence or microthrombotic ischemic liver injury[29]. Although respiratory symptoms are the most reported among COVID-19 patients, these pulmonary manifestations are vulnerable to decompensated liver cirrhosis but are currently understudied. A cohort study with 250 patients with prior CLDs reported high mortality in patients with cirrhosis (RR: 4.6, 95.0%CI: 2.6-8.3)[28]. In an international study, a positive correlation was shown that patients with cirrhosis are predisposed to significant toxic liver injury due to SARS-CoV-2 infection, as acute-on-chronic liver failure had occurred in 20.0% of patients who experienced severe cirrhosis with COVID-19[28]. The viral ability of SARS-CoV-2 to bind to ACE-2 receptors on epithelial cells of the bile duct demonstrates its ability to affect liver regeneration capabilities and immune response[28]. By affecting the innate immunity of the reticuloendothelial system, the immunosuppressed state causes a cytokines-mediated reaction, resulting in liver decompression[28].

COVID-19 effect on liver cancer

Pre-existing liver diseases are considered risk factors for poorer prognosis in COVID-19 as various pathophysiological processes result in liver damage due to SARS-CoV-2 infection. Biochemical presentations of liver injury include elevated levels of ALT/AST, ALP, GGT, or total bilirubin above the normal range. The decrease in lymphocyte count and the increase in neutrophil counts demonstrate the role of innate immunity in COVID-19-associated hepatic injury. Postmortem studies in liver histology in COVID-19 patients show moderate microvascular and macrovascular steatosis with mild inflammation of the lobular portal. This highlights the pathological changes observed in hepatocellular carcinoma (HCC). Elevated levels of eosinophils are observed in autopsy studies in centrilobular steatosis, in addition to the increased number of mitotic cells[30]. Patients with HCC are closely monitored, as increased inflammation due to COVID-19 may predispose patients to post-hepatectomy liver failure. Furthermore, COVID-19 can potentially exacerbate CLD and alter treatments for cancer patients with a higher risk of infection and poor outcomes[30]. The management and monitoring of patients with HCC

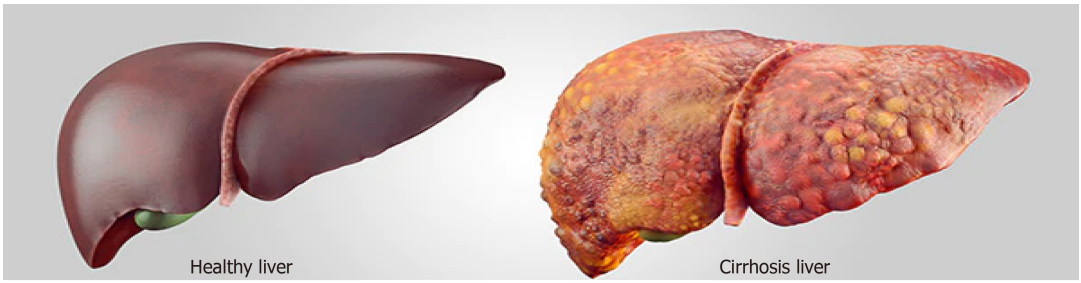

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Figure 2 Healthy and cirrhosis liver.

are performed by imaging (magnetic resonance imaging, ultrasound) and measuring alpha-fetoprotein levels[29]. The practice guidelines recommend the establishment of surveillance intervals to reduce the radiologic capacity of at-risk patients, with a 98.0% estimate that at-risk patients would not develop HCC during each surveillance interval. Locoregional and systematic therapies are recommended for advanced HCC treatment. However, oral therapy with tyrosine kinase inhibitors (*i.e.*, sorafenib and lenvatinib) and immunotherapy effectively serve as first-line therapies to reduce exposure[29].

COVID-19 effect on liver transplantation

With the severity of SARS-CoV-2 infection dependent on comorbidities (*i.e.*, cardiovascular disease and diabetes mellitus), underlying liver diseases do not necessarily influence the outcome of COVID-19 infection. Solid-organ transplants, including liver transplant (LT) recipients, are increasingly susceptible to severe infections due to chronic immunosuppression, thereby increasing the risk for severe COVID-19 infection. A meta-analysis that included 17 articles and the outcomes of 1481 COVID-19 LT patients was compared with 239704 non-LT patients infected with COVID-19. From 17 articles, a cumulative incidence of mortality of 17.4% (95.0%CI, 15.4-19.6) was found among LT recipients with COVID-19 with causes of death reported as 62.54% by COVID-19-related complications (95.0%CI, 56.24-68.55), 29.88% by pulmonary failure (95.0%CI, 24.28-36), and 1.6% liver-related (95.0%CI, 0.1-2.84). Mortality was proportionate between LT and non-LT patients [OR, 0.8 (0.6-1.08); $P = 0.14$][31]. Twelve studies in the same meta-analysis reported that 23.0% of LT patients who had developed a severe COVID-19 infection were positive with symptoms that included fever (49.7%), cough (43.76%), dyspnea (29.27%), and symptoms gastrointestinal (27.26%)[31]. Eight studies from the same meta-analysis reported modification change immunosuppression in 55.9% of LT recipients infected with COVID-19[31]. Comorbidities such as hypertension, diabetes, and obesity were common in infected patients where 72.0% of the patients were hospitalized, and 16.0% required care in the intensive care unit (ICU)[31]. Although hospitalization of LT recipients far exceeded non-LT patients [OR, 1.99 (1.41-2.8), $P < 0.001$], the ICU care requirement was comparable between groups, as the cumulative incidence of graft dysfunction was 2.3% (1.3-4.1)[31].

COVID-19 effect on non-alcoholic fatty liver disease

Many observational studies have shown that patients with comorbidities such as cardiovascular disease, arterial hypertension, diabetes mellitus, CLD, or cancer are susceptible to more severe episodes of COVID-19, as seen in NAFLD and other less common disorders[32]. Recently, several meta-analyses have shown that obesity and diabetes (both strongly associated with NAFLD) are significantly associated with the progression of more severe disease and increased mortality in patients with COVID-19[32]. They have reported a six-fold increased risk of severe COVID-19 in the presence of obesity in NAFLD. In addition, a meta-analysis showed that obesity could exacerbate COVID-19 infection. Patients with severe COVID-19 disease had higher body mass indices, and obesity was associated with the development of the disease, the need for care, and admission to an ICU[32]. The risk of severe COVID-19 in obese patients was more significant than in younger patients. This suggests that NAFLD patients are at increased risk of liver damage, although liver enzyme levels at admission or during hospitalization were generally not significantly elevated. Furthermore, NAFLD was not associated with adverse clinical outcomes in younger patients with COVID-19. Another study found that NAFLD was more common in patients with severe COVID-19 than in stable patients. However, the mean age and the number of comorbidities were also significantly higher in patients with severe COVID-19 infections[32]. Patients with NAFLD had a substantially higher risk of disease progression, more likely changes in liver enzymes, and longer viral shedding times than non-NAFLD patients. Non-NAFLD patients showed that moderate to high Fibrous-4 and NAFLD fibrosis scores were strongly and independently correlated with the severe progression of COVID-19 disease[32].

COVID-19 effect on alcoholic liver disease

The ACE-2 receptor is exceedingly expressed in alveolar type II cells and liver and bile duct cells, making it significantly feasible for SARS-CoV-2 to infect cells in those areas. Especially, cholangiocytes have a specific ACE-2 receptor in more concentrations than hepatocytes, making them more susceptible to COVID-19 infection. However, because the liver harbors a widespread quantity of macrophages, generating an ample cytokine-mediated immune reaction, hepatocytes can also be prone to a SARS-CoV-2 infection. Patients with COVID-19 patients with liver cirrhosis have always shown elevated levels of ALT, AST, D-dimer, CRP, IL-6, and ferritin. Although the current literature is limited, research has proven that people with CLDs could have increased models for end-stage liver disease and undergo extended liver and pulmonary complications while infected with COVID-19. Specifically, the mortality rate in patients with preexisting liver disease is 1.8%. Lastly, the severity of liver harm due to COVID-19 infection tends to be substantially worse and more widespread in people with pre-existing alcoholic liver cirrhosis than in those without[33].

ANTI-SARS-CoV-2 TREATMENTS EFFECTS ON THE LIVER

Currently, various treatments for COVID-19 (SAR-CoV-2) are being investigated, some of which may be associated with hepatotoxicity[34]. Remdesivir (RDV), an antiviral medication, was initially developed and tested for the treatment of hepatitis C and later the Ebola and Marburg viruses. Amid the COVID-19 pandemic, RDV was approved for emergency use to treat COVID-19 in many countries[35]. In patients diagnosed with COVID-19, *in vitro* and *in vivo* studies indicate that RDV has an antiviral effect on SARS-CoV-2[36]. Various medication-related adverse events include but are not limited to reasonable degrees of nausea and vomiting, headache, fatigue, renal dysfunction, and rash[37]. The risk of an adverse event involving the liver exists as one of the clearest potential risks from RDV[38]. RDV therapy is administered intravenously for 3 to 10 d and is often accompanied by reversible mild to moderate elevations in serum AST levels, but has been rarely associated with clinically apparent liver injury. Effects on the liver range from asymptomatic to mild-with elevations in serum ALT and AST upon introduction of RDV therapy in patients with COVID-19. The systemic effects of COVID-19 likely overshadow the outcomes of hepatic involvement[37]. However, there is uncertainty regarding if the effect on liver enzymes is due to remdesivir, COVID-19 solely, or both[39,40]. It is recommended that patients remain under the supervision of health professionals to monitor liver health before and during remdesivir infusions[37]. To fully assess the risk of remdesivir-associated liver damage, more studies are necessary for this area[40]. Lopinavir (LPV) is an antiretroviral protease inhibitor, used together with ritonavir (booster) in the prevention and treatment of human immunodeficiency virus (HIV) infection[41]. Lopinavir/ritonavir (LPV/r) was developed to inhibit HIV protease, the primary distinction for the SARS-CoV-2 counterpart (3CLpro) lies within the varying spatial structure of the HIV aspartic protease as compared with 3CLpro cysteine protease[41]. The LPV/r combination improves LPV pharmacokinetics by decreasing liver metabolism by inhibiting the cytochrome (CYP) P450 3A4 enzyme[41].

A randomized controlled study in adult patients hospitalized with COVID-19 shows that of those adults treated with LPV/r, only one individual in the LPV/r group presented elevated ALT, more than 2.5 times above the normal limit[41,42]. When comparing patients treated with LPV/r to patients in the control group, there was no evidence of liver dysfunction noted in controls. It is important to acknowledge that the patient presenting with an elevated ALT had a pre-existing chronic liver condition, possibly contributing to the liver disturbance[42]. Another research study suggests that no observable side effects were found in the LPV/r group, except for transient elevation of ALT elevation (< 125 U/L) in three patients[43]. Given that none of the patients progressed to a severe clinical status at the end of the follow-up period, it is believed that LPV/r treatment rarely causes harm in patients recovering from COVID-19[42]. LPV/r is considered an independent factor for liver injury[44]. Interferons (IFNs) are natural antiviral immune modulators that help the body's immune system defend against infection and disease, including viruses and cancer[45]. Studies have shown that during SARS and middle east respiratory syndrome, Type I IFNs are markedly suppressed and the administration of exogenous Type I IFNs has been shown to reduce the severity of the symptoms of these diseases[46]. To assess the effectiveness and safety of interferon β-1a (IFN β-1a) in patients with severe COVID-19, a randomized clinical trial was conducted[47]. Comparisons were made between patients receiving IFN and those receiving controlled standard therapy. Hepatic complication rates were measured between patients in the treatment group and those patients receiving standard care while the preexisting liver disease was considered[44]. The frequency of hepatic failure did not differ between the IFN and control groups (11.90% *vs* 23.07%), suggesting that IFN-β-1a may not be a major factor in the liver damage seen by COVID-19 patients[47]. Studies show that IFNs used to treat patients with COVID-19 are unlikely to be associated with liver disease. IFNs may lead to hepatic toxicity when combined with other drugs[44]. To authenticate these results, additional studies are necessary[44]. Baricitinib is a JAK-STAT inhibitor used to treat individuals with rheumatoid arthritis who cannot tolerate more than one tumor necrosis factor (TNF) antagonist[6]. By decreasing adaptor-associated kinase 1 activity, a regulator of clathrin-

mediated endocytosis, baricitinib has been shown to affect the hyperinflammatory state that developed during SARS-CoV-2 infection and may prevent endocytosis and viral infection[6,48]. Furthermore, the oral administration of baricitinib and the excellent pharmacokinetic profile (very short half-life, low plasma protein binding, and minimal interference with CYP enzymes) make it a viable combination therapy with direct-acting antivirals such as LPV/r and RDV[48]. The growing number of reports of infections and thrombosis following the use of JAK inhibitors for the treatment of COVID-19 should be taken seriously as liver damage, cholestasis, and hepatitis unexpectedly manifested in a non-negligible fraction of individuals[6]. Furthermore, these unfavorable hepatic consequences should be evaluated. Tocilizumab is a monoclonal antibody that is used to block the inflammatory protein IL-6. Tocilizumab improves joint pain and swelling from arthritis and reduces other symptoms caused by inflammation. More recently, tocilizumab use has been indicated for the treatment of cytokine release syndrome in patients with COVID-19 infection[49]. Common side effects of tocilizumab include a runny or stuffy nose, sinus pain or sore throat, headache, or dizziness. The most common side effects of tocilizumab include headache and hypertension but, rarely, hepatotoxicity ranging from mild transaminase elevation to severe drug-induced liver injury can occur[50].

SARS-CoV-2 VACCINES EFFECT ON THE LIVER

It is not yet clear whether RNA or DNA-based vaccines have any direct effect on the liver, resulting in hepatotoxicity. Although anti-coronavirus treatments have been found to cause mitochondrial and endoplasmic reticulum dysfunction, the effects of vaccines require further testing[6]. Patients receive what are often considered benign mRNA vaccines for Crigler-Najjar syndrome and rabies, which have some form of hepatotoxicity. While there is no definitive cause, there seems to be a potential link between the two. This is not the case with DNA vaccines, which makes them strikingly different. Immune system stimulation occurs *via* a completely different mechanism than mRNA vaccines, with IFN-1 secretions triggering the immune response. Unlike mRNA vaccines, DNA vaccines do not require subsequent doses to maintain monoclonal antibody protection, making DNA vaccines not only potentially more efficacious than mRNA vaccines, but requiring lower amounts to achieve a less toxic overall therapeutic effect. More research is needed to fully understand the mechanisms involved and how they affect the liver. Existing studies exclude patients with chronic liver disease as they are contraindicated by mRNA vaccines, making little information available regarding the pathophysiology, and comparing that of otherwise healthy individuals[6]. Patients with CLD are at an increased risk of infection, which is expected given the insufficient immune response. Vaccinations are imperative to reduce mortality in patients with CLD[51]. According to the Advisory Committee on Immunization Practices (ACIP), patients with CLD should be vaccinated against SARS-CoV-2 and influenza, pneumococcus, tetanus, diphtheria, pertussis, herpes zoster, hepatitis A, and hepatitis B[52]. Specifically, with the COVID-19 vaccine, ACIP suggests an mRNA vaccine with a booster dose five months after completing the two scheduled doses. For severely immunosuppressed patients, a booster dose is recommended after three months to strengthen the immune response[53]. A double-blind randomized trial studying the administration of a third dose of the mRNA vaccine in transplant recipients showed a strong immune response compared to the placebo group[54]. In a case report of healthy patients with no history of liver disease, patients developed jaundice and elevated liver enzymes after administration of the mRNA vaccine, either after the first or second dose. In these cases, the laboratory values and symptoms resolved without treatment after several weeks. The data suggests that this response is due to a neutrophil-predominant inflammatory response[55]. Comparatively, much data shows contraindications to multiple COVID-19 vaccines, including booster doses, specific to CLD patients. Data are still needed to assess the efficacy and long-term effects of multiple COVID-19 vaccines in patients with CLD.

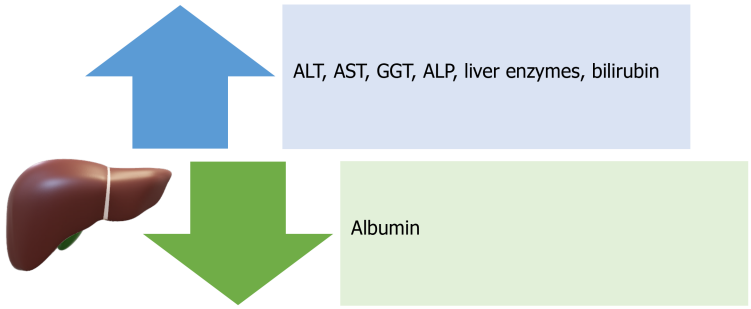
The severity of the liver disease may be assessed using the Child-Pugh scale. This scale anticipates mortality in CLD and is categorized into three stages: good hepatic function, moderately impaired hepatic function, and advanced hepatic dysfunction[56]. Multiple factors, including the stage of CLD, can be a determinant of the efficacy of a vaccine, and those in later stages are more susceptible to infections and adverse events. This is possibly due to the inefficiency of the body in producing an adequate immune response[51]. However, the World Health Organization (WHO) currently recommends that COVID-19 vaccines for those with deficient immune systems be given additional boosters to help increase a sufficient immune response[57]. It is recommended that vaccinations be administered as early in the disease process as possible to gain the best performance of the vaccine[52]. In a study on the antibody response of the vaccine in CLD patients, subjects were given the recommended series of the mRNA vaccine. The results showed that 24.0% of the subjects had a poor antibody response[58]. Additional research is needed to further assess the success of the vaccine in varying severities of CLD.

DISCUSSION

Lessons from previous coronavirus outbreaks and other viral epidemics indicate that the combination of systemic and partial inflammatory responses induced by these infections may result in severe respiratory syndromes and related complications (such as abnormal liver function, cardiac insufficiency, and renal failure)[6]. Manifestations of liver damage from SARS-CoV-2 include a decrease in albumin and an increase in ALT, AST, liver enzymes, and bilirubin[9]. Increases in GGT and ALP are also seen in COVID-19 patients, indicating liver damage to bile duct cells[7] (Figure 3). Since liver biopsies taken from a small number of COVID-19 patients did not reveal viral inclusions, but rather a macro-vesicular steatosis, liver damage may also be the result of bile duct cell damage[59]. The pathogenic alterations frequently take the form of macro-vesicular steatosis and mild lobular and portal inflammation[59,60]. According to earlier research, severe instances of coronavirus infection had a strikingly higher frequency and severity of liver impairment than moderate cases. The mechanism by which coronaviruses harm hepatocytes and influence hepatic function is still unknown, even though multiple clinical studies have shown a high link between coronaviruses and liver damage[6]. Potential mechanisms of liver injury that have been reported include immune-mediated damage because of the severe dysregulated inflammatory response, direct cytotoxicity, systemic hypoxia with hypoxic hepatitis, drug-induced liver injury, reactivation of pre-existing liver disease, mitochondrial dysfunction, SARS-CoV-2-induced hepatic steatosis, microthrombotic disease, ischemic hepatitis, cardiomyopathy with hepatic congestion, and extrahepatic release of transaminases[61]. Ischemic, hypercoagulable, and hyperinflammatory states are independent predictors of death in patients with COVID-19 and not liver injury[62]. Coronavirus infection significantly increases immunological activation. Numerous cytokines and chemokines (IL-6, IL8, IFN, and TNF, among others) are generated by immune cells after coronavirus infection and released into the blood, causing inflammation in different organs or even acute respiratory distress syndrome and multiple organ failure, suggesting that coronavirus-induced systemic inflammatory response syndrome (SIRS) and cytokine storms are important causes of liver damage[6,25]. This shows that immunotherapy is necessary for individuals with coronavirus infection, and as a result, corticosteroids and interferons are frequently utilized due to their ability to reduce inflammation[6]. Hypoxia may result in a long-term increase in reactive oxygen species, which may encourage the release of a variety of inflammatory mediators that harm the liver[6,25]. As a result, it will be important to keep an eye on patients' hypercoagulable conditions, such as thrombocytopenia and elevated levels of D-dimer and ALP, to prevent thrombosis and additional ischemia and hypoxia[6,23].

Immune compromise is typically caused by hepatitis B and C, liver cirrhosis, liver malignancy, and immunosuppressive medications after liver transplantation[6]. The severity and mortality rate in HBV infection patients are higher than in those with negative HBV due to delayed clearance of SARS-CoV-2 [6]. The Child-Pugh scores of those who have already developed liver cirrhosis are likely to rise due to liver injury caused by COVID-19[56]. Furthermore, COVID-19 complications occur earlier and to a greater extent in patients with systemic immunocompromised status[6]. COVID-19 also has a significant impact on the treatment of liver diseases[11]. The discontinuation of high-dose corticosteroid therapy in hepatitis B and C patients receiving anti-HBO treatment may result in HBV reactivation during SARS-CoV-2 infection[6]. In addition, lopinavir and ritonavir have been shown to increase the risk of developing liver injury in HBV or HCV infection patients[6,11]. Coronavirus infection is currently treated with redelivering, lopinavir/ritonavir, interferon-a, baricitinib, and tocilizumab. The difficulty in developing optimized drugs for coronavirus infection is mainly due to severe side effects. Remdesivir, lopinavir, and ritonavir have all been linked to an increased risk of liver injury, with the severity of the injury being closely related to the dose of these drugs. IFNs have the potential to trigger a non-specific immune response, resulting in hepatocyte damage and autoimmune hepatitis, as well as an increased risk of developing severe complications such as systemic inflammatory reaction syndrome and acute respiratory distress syndrome[6]. Baricitinib, as a JAK inhibitor, can increase the risk of thrombosis and cause liver damage[6,48]. Tocilizumab can also reactivate HBV in SARS-CoV-2 co-infection, causing both viral hepatitis and COVID-19 recovery to be delayed; whereas other studies have shown hepatotoxicity as a potential side effect[50]. Overall, coronavirus vaccines will be critical in preventing outbreaks, but several factors must be considered to avoid an activated innate inflammatory response, an increase in the incidence of autoimmune diseases, and vaccine-induced liver injury[6].

Furthermore, a study observed 900 patients (32.2% in the 18-39 age group, 39.7% in the 40-69 age group, and 28.1% in the 70+ age group) with SARS-CoV-2[63]. It was seen that those with comorbidities, median D-dimer, and CRP levels all increased with age. AST/ALT and ALP/GGT levels also increased significantly during COVID-19[63]. Patients with elevated hepatocellular transaminases (AST/ALT) and cholestasis parameters (ALP/GGT/bilirubin) were found in 40.3% (n = 262/650) and 45.0% (n = 287/638), respectively[61]. Importantly, patients between the ages of 40 and 69 were more likely to experience COVID-19-associated liver injury (16.0%, $P < 0.001$), abnormal liver chemistry, and liver-related death (6.5%, $P < 0.001$)[61]. After the initial SARS-CoV-2 polymerase chain reaction result was positive, elevated AST and bilirubin levels independently predicted mortality in the entire population and patients aged 40 to 69 years[63].



DOI: 10.5501/wjv.v12.i2.109

Figure 3 Manifestations of liver damage from severe acute respiratory syndrome coronavirus 2. ALT: Alanine transaminase; AST: Aspartate transaminase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase.

CONCLUSION

The incidence of liver injury in patients with COVID-19 has been estimated to be as high as 53.0%. Those affected by COVID-19-associated liver injury generally fall between the ages of 40 and 69. The mechanism by which SARS-CoV-2 damages hepatocytes is still unclear. However, the SARS-CoV-2 virus may play a direct role in liver damage because both healthy individuals and those with preexisting liver disease exhibit abnormal LFTs. The liver injury caused by COVID-19 is related to the degree of severity of the infection and manifests itself with different degrees of liver abnormalities. The degree of liver injury manifested by AST, ALT, total bilirubin, GGT, and ALP has been shown to have a positive correlation with the severity of the disease. Interestingly, some studies have even shown that mortality correlates with elevated AST and low albumin levels. Furthermore, SIRS and cytokine storms augment liver injury and dysfunction. Commonly used medications may play a role in liver hepatotoxicity, however further studies are necessary. Pre-existing liver diseases are considered risk factors for worse prognosis in COVID-19, specifically, liver cirrhosis was shown to increase the mortality in these patients. Although vaccines have significantly changed the course of this pandemic, CLD is a contraindication of multiple COVID-19 vaccines. However, the increased severity of liver disease in determining the immune response to the COVID-19 vaccine is still unclear, and more studies are required in this area. As more information about the virus becomes available, it will be critical to comprehend the pandemic's effects on the liver, as well as the possible long-term consequences, especially in the immunocompromised population.

FOOTNOTES

Author contributions: Sanyaolu A did the conceptualization and methodology; Abbasi AF, Prakash S, Patidar R, Desai P, Williams M, Jan A, Hamdy K, Solomon R, Balendra V, Shazley O, Khan N, Annan R, Ansari M, and Dixon Y did the writing-original draft preparation; Okorie C, Antonio A and Marinkovic A writing–review and editing the study; Marinkovic A did the project administration.

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ORIGINAL ARTICLE

Observational Study

Demographic and risk characteristics of healthcare workers infected with SARS-CoV-2 from two tertiary care hospitals in the United Arab Emirates

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Abstract

BACKGROUND

Understanding the transmission dynamics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among healthcare workers (HCWs) and their social contacts is crucial to plan appropriate risk-reduction measures.

AIM

To analyze the socio-demographic risk factors and transmission of SARS-CoV-2 infection among HCWs in two tertiary care hospitals in Dubai, United Arab Emirates.

METHODS

The demographic and clinical characteristics were available for all HCWs in both facilities from the human resources department. A cross-sectional survey was conducted from January-April 2022 among HCWs who tested positive through

Reverse Transcriptase Polymerase Chain Reaction of the nasopharyngeal swab for SARS-CoV-2 between March 2020 and August 2021 in two tertiary-level hospitals. The survey included questions on demographics, work profile, characteristics of coronavirus disease 2019 (COVID-19), and infection among their household or co-workers. The survey also checked the knowledge and perception of participants on the infection prevention measures related to SARS-CoV-2.

RESULTS

Out of a total of 346 HCWs infected with SARS-CoV-2, 286 (82.7%) HCWs consented to participate in this study. From the sample population, 150 (52.5%) of participants were female, and a majority (230, 80.4%) were frontline HCWs, including 121 nurses (121, 42.4%). Only 48 (16.8%) participants were fully vaccinated at the time of infection. Most infected HCWs (85%) were unaware of any unprotected exposure and were symptomatic at the time of testing (225, 78.7%). Nearly half of the participants (140, 49%) had co-infection among household, and nearly one-third (29.5%) had co-infection among three or more household. Another 108 (37.8%) participants reported cross-infection among co-workers. The frontline HCWs were significantly more infected (25.1% *vs* 8.6%, $P < 0.001$) compared to non-frontline HCWs. Another significant risk factor for a high infection rate was male sex ($P < 0.001$). Among the infected frontline HCWs, a significantly higher proportion were male and shared accommodation with family ($P < 0.001$). COVID-19 vaccination significantly reduced the infection rate (83.2% *vs* 16.8, $P < 0.001$) among HCWs. Most participants (99.3%) were aware about importance of appropriate use of personal protective equipment. However, only 70% agreed with the efficacy of the COVID-19 vaccination in preventing an infection and severe disease.

CONCLUSION

The risk profiling of the HCWs infected with SARS-CoV-2 found that working at frontline and being male increase the rate of infection. COVID-19 vaccination can effectively reduce the rate of transmission of SARS-CoV-2 among HCWs.

Key Words: Coronavirus disease 2019; Risk factors; Disease transmission, infectious; Infectious disease transmission, Professional-to-patient; Health personnel; Socioeconomic factors

Core Tip: The healthcare workers (HCWs) are vulnerable to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In the current study, the authors found that the frontline and male HCWs were at higher risk of infection. Among the infected frontline HCWs, a significantly higher proportion were male and staying in a rented accommodation with family. The coronavirus disease 2019 vaccination is effective in preventing the transmission of SARS-CoV-2 among HCWs. This information can be utilised for the healthcare workforce management and to formulate strategies to mitigate the risk of transmission of SARS-CoV-2 to the HCWs.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has overwhelmed the healthcare resources across the globe. Since the inception of the pandemic, reports have been published on the increased vulnerabilities of healthcare workers (HCWs) compared to the general community for infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1,2]. A prospective cohort study conducted among 99795 HCWs reported that the HCWs are at a threefold higher risk of acquiring COVID-19 compared to the general community. However, the risk of exposure is not uniform and depends on multiple factors, such as the nature of work (frontline), race or ethnicity (Black, Asian, and other ethnic minorities), and access to or reuse of the personal protective equipment (PPE)[1]. Besides the risk of illness, the HCWs are at considerable risk of adverse mental health during the COVID-19 pandemic[3]. Moreover, the social and household contacts of the HCWs are also potentially vulnerable to SARS-CoV-2 infection[4].

On the other hand, the absenteeism of HCWs from work is further detrimental to the already stretched healthcare services during the pandemic[5].

From the start of COVID-19 pandemic, the experts strongly expressed concerns regarding the nosocomial transmission of SARS-CoV-2[6,7]. HCWs were assumed to play a pivotal role in the transmission chain during a nosocomial outbreak of SARS-CoV-2. However, limited information exists on the transmission characteristics and dynamics of SARS-CoV-2 infection among the HCWs or their social contacts. In this scenario, it is crucial to explore the dynamics of SARS-CoV-2 transmission among the HCWs and their social contacts to develop and implement appropriate risk-reduction measures[6].

In the current study, the authors performed a retrospective analysis of HCWs infected with SARS-CoV-2 to analyze the socio-demographic risk factors and the characteristics of SARS-CoV-2 infection among HCWs and their social contacts.

MATERIALS AND METHODS

The demographic and clinical characteristics were available for all HCWs in both facilities from the human resources department. A cross-sectional survey was conducted between January and April 2022 among the HCWs who tested positive for reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 between March 2020 and August 2021 in two multi-specialty tertiary-level hospitals located in Dubai. The cross-sectional survey was conducted to extract further information from the infected HCWs on their social contacts, including household. The survey included Multiple-Choice Questions and questions with 5-point Likert scale. The survey questionnaire, attached in the Supplementary material, has a total of three sections: (1) Demographic details of the participants, including age, gender, department, nature of work, and COVID-19 vaccination status; (2) Details about SARS-CoV-2 infection, the reason for RT-PCR testing, severity and duration of the symptoms, and infection among their household contacts and co-workers; and (3) Knowledge and perception among the participants on PPE and infection prevention measures related to SARS-CoV-2. The human resource department, who were not part of the data analysis, sent the survey questionnaire through e-mail. The identity of the participants was kept confidential. Frontline HCWs were those who provide care for patients with COVID-19 or worked in areas with direct patient contact during the pandemic. As per the local health regulatory requirements, the HCWs were tested with RT-PCR only in case of symptomatic infections, contact tracing, or pre-travel screening during this period. The study considered only the first SARS-CoV-2 infection for further analysis. In the United Arab Emirates (UAE), seven COVID-19 vaccines were approved for use and are made available to the public for free of cost. The data on the average number of new cases in the community was extracted from the website of National Emergency Crisis and Disaster Management Authority, UAE (https://covid19.ncema.gov.ae/en). The study was approved by the scientific and ethical committee of the hospital and Dubai Scientific Research Ethics Committee (DSREC/09/2020_32).

Statistical analysis

Descriptive statistical analysis was conducted for frequencies, percentages, medians, and ranges. Continuous data was presented as mean [standard deviation (SD)] or median with Interquartile Range (IQR). Two groups were compared in this study using the 2-sample test for equality of proportions with continuity correction (Chi-square). A comparison was made between the categorical paired data with McNemar Test. The authors used Fisher exact test to compare less than five-count cells. All the tests were 2-tailed, and $P < 0.05$ was considered to be significant. The statistical analyses were conducted using R version 3.4.2 from the Comprehensive R Archive Network (R Core Team, 2020).

RESULTS

Out of a total of 1568 HCWs working in both hospitals, 346 (22.1%) tested positive for SARS-CoV-2 RT-PCR during the study period. Amongst this study population, 16 (4.6%) HCWs were found to be re-infected with SARS-CoV-2. However, as mentioned earlier, only the first infection was considered for the analysis. From the 346 infected HCWs, 286 (82.7%) HCWs agreed to participate in the cross-sectional survey. Amongst the participants, 150 (52.5%) were female, whereas a majority of the participants (230, 80.4%) were frontline HCWs, including 121 nurses (121, 42.4%). Only 48 (16.8%) participants were fully vaccinated at the time of infection.

Most of the participants (225, 78.7%) were symptomatic at the time of RT-PCR testing. Among the asymptomatic HCWs, 35 (12.2%) were tested for close contact tracing. Nearly half of the participants (140, 49%) had a co-infection with their household contacts. Moreover, half (48, 51.6%) of the infection in the households occurred in a single person, while nearly one-third (29.5%) had infection among three or more households. Further, 108 (37.8%) participants reported cross-infection among their co-workers (Table 1).

Table 1 Descriptive data on demographic and risk-profile of the healthcare workers infected with severe acute respiratory syndrome coronavirus 2

Variables		*n* (%)
Age, yr		36 (IQR-10)
Female		150 (52.5)
Staff travelling in hospital accommodation		454/1467 (29)
Work profile of healthcare workers	Doctor	34 (11.9)
	Nurses	121 (42.4)
	Technician	37 (12.9)
	Pharmacy	11 (3.8)
	Paramedical staff	10 (3.5)
	Non-clinical staff	73 (25.5)
Reason for testing with RT-PCR	Symptomatic	225 (78.7)
	Contact tracing	35 (12.2)
	Travel screening	8 (2.8)
	Other	18 (6.3)
Severity of COVID-19	Asymptomatic	36 (12.6)
	Mild	220 (76.9)
	Moderate	25 (8.7)
	Severe	5 (1.7)
Place of isolation	Institutional	50 (17.4)
	Home isolation	189 (66.1)
	Hospitalization	49 (17.1)
Symptom duration	< 1 wk	99 (34.6)
	1-2 wk	128 (44.8)
	2-3 wk	49 (17.1)
	> 3 wk	10 (3.5)
Pre-existing chronic illness	Diabetes Mellitus	33 (11.5)
	Hypertension	31 (10.8)
	Chronic respiratory disease	6 (2.1)
	Chronic kidney disease	2 (0.7)
	Other	4 (1.4)
	None	210 (73.5)
HCWs with households infected within 14 d	Total	140 (49)
	Earlier (3-14 d)	49 (35)
	Same time (within 2 d)	55 (39.3)
	Later (3-14 d)	36 (25.7)
Number of infected households	1	48 (51.6)
	2	18 (18.9)
	3	16 (16.8)
	> 3	12 (12.7)
HCWs with co-workers infected within 14 d	Total	108 (37.8)
	Earlier (3-14 d)	38 (35.2)

	Same time (within 2 d)	33 (30.5)
	Later (3-14 d)	37 (34.3)
Number of infected co-workers	1	23 (24.2)
	2	16 (16.8)
	3	3 (3.1)
	> 3	17 (17.9)

COVID-19: Coronavirus disease 2019; HCWs: Healthcare workers; RT-PCR: Reverse transcriptase polymerase chain reaction.

When compared between the infected and the uninfected HCWs, frontline HCWs (25.1% *vs* 8.6%, $P < 0.001$), who were males (54% *vs* 46%, $P < 0.001$) recorded a significantly high infection rate. The infection rate among the unvaccinated HCWs (83.2% *vs* 16.8%, $P < 0.001$) was nearly five times higher than those HCWs who were vaccinated against COVID-19. The study found that the type of accommodation (self-owned *vs* hospital sponsored) showed no significance effect on the infection rate (Table 2). A significantly high proportion of the infected frontline HCWs were males who stayed in rented accommodation with family ($P < 0.001$) (Table 3). Finally, the trend chart of a month-wise comparison of the infected HCWs and the average new cases in UAE showed three peaks.

The survey also tried to assess the knowledge and perception of the participants about safety precaution, vaccination, and the disease. Most of the participants were aware about the appropriate usage of PPE (99.3%) and did not agree to unprotected exposure to a patient with COVID-19 (85%). Around 74% of the participants agreed with the importance of social precautions like face mask, social distancing, and hand hygiene in preventing the SARS-CoV-2 infection. Only 70% agreed on the efficacy of COVID-19 vaccination in preventing infection or progression to the severe disease. The deficiency of PPE at the workplace was reported by 23.4% of the participants, whereas 29.7% participants wanted an improvement in the quality and availability of the PPE (Table 4).

DISCUSSION

This cross-sectional analysis of RT-PCR-positive HCWs from two tertiary care hospitals showed that frontline HCWs had a significantly higher infection rate. The study infers that being a male is a significant risk factors for getting infected with COVID-19. Among the infected frontline staff, a significantly higher proportion were male who shared their accommodation with family members. COVID-19 vaccination was effective in reducing the rate of infection among HCWs.

From the start of COVID-19 pandemic, various studies recorded a higher infection rate among the frontline HCWs. The risk was higher due to the reuse or inadequate availability of the PPEs and due to which the studies advocated strategies like access to high-quality PPEs and early COVID-19 vaccination to curb the spread of the virus[2,8]. Nearly one-fourth of the participants in this study reported insufficient access to the PPEs, while most were unaware of any unprotected exposure with COVID-19 patients. Limited access to adequate PPE has been linked with higher odds of infection[9-11]. Hence, ensuring access to high-quality PPEs for HCWs is an important workplace risk-reduction measure. The rate of infection was significantly higher among the male HCWs as found in other studies[2,12].

Around 13% of the study participants had asymptomatic infection. The number of asymptomatic infections could have been higher, if the hospitals had routine surveillance testing for the HCWs. However, the impact of the routine surveillance testing of asymptomatic HCWs in preventing nosocomial transmission of SARS-CoV-2 is unknown[13]. A consensus experts' panel recommended testing the HCWs to get tested for SARS-CoV-2 only when they are symptomatic or when they encountered unprotected exposure over routine testing[14].

Around 38% of the infected participants agreed to infection among their co-workers within 14 days of their own infection, and nearly one-fifth of them agreed to have three or more infected co-workers. Moreover, sharing accommodation with family or friends was significantly higher among the infected frontline HCWs. In the absence of epidemiological investigation and genomic sequencing, these infections cannot be segregated as an outbreak. However, the absenteeism of multiple HCWs from the same department can disrupt the services of already overwhelmed frontline departments during the pandemic. Despite various published reports on a nosocomial outbreak of SARS-CoV-2, ambiguity exists regarding the role of HCWs in initiating or amplifying the nosocomial outbreaks[6,15].

Most epidemiological research on SARS-CoV-2 infection among the HCWs has focused on transmission dynamics within the hospital setting. However, the research on the impact of social-cultural and demographic factors on the transmission of SARS-CoV-2 among HCWs is lacking. Recently, a large prospective study conducted in the United Kingdom found the effect of socio-demographic characteristics on the risk of infection among the vulnerable HCWs. The study found that

Table 2 Comparison of risk-factors among infected and non-infected healthcare workers, *n* (%)

	Uninfected HCWs, *n* = 1282	Infected HCWs, *n* = 346	*P* value
Accommodation			
Hospital sponsored	381 (29.7)	89 (25.9)	0.15
Self-owned	901 (70.3)	257 (74.1)	(χ^2 statistic value, 2.12)
Work profile			
Frontline	689 (53.7)	278 (80.4)	< 0.001
Non-frontline	593 (46.3)	67(19.6)	(χ^2 statistic value, 81.19)
COVID-19 vaccination			
Vaccinated	1198 (93.2)	58 (16.8)	< 0.001
Unvaccinated	88 (6.8)	287 (83.2)	(χ^2 statistic value, 895.49)
Sex			
Male	511 (39.9)	187 (54.0)	< 0.001
Female	771 (60.1)	159 (46.0)	(χ^2 statistic value, 22.38)

COVID-19: Coronavirus disease 2019; HCWs: Healthcare workers.

Table 3 Comparison of demographics among frontline *vs* non-frontline healthcare workers infected with severe acute syndrome coronavirus 2, *n* (%)

	Frontline healthcare workers, *n* = 238	Non-Frontline healthcare workers, *n* = 48	*P* value
Accommodation			
Shared with family	167 (70.2)	23 (47.9)	< 0.001
Shared with friends	60 (25.2)	24 (50)	(χ^2 statistic value, 31.07)
Non-shared	11 (4.6)	1 (2.1)	
Accommodation			
Self-rented	140 (58.8)	18 (11.4)	< 0.001
Hospital provided	49 (20.6)	25 (33.8)	(χ^2 statistic value, 42.68)
Others	49 (20.6)	5 (9.3)	
Sex			
Male	205 (86.1)	35 (72.9)	0.02
Female	33 (13.9)	13 (27.1)	(χ^2 statistic value, 5.17)

amongst the demographic and household risk factors, young age, living with a co-worker, and high religiosity are associated with high infection odds among the HCWs[9]. In another study, high odds of infection were observed among the HCWs from community contact with a suspected or a confirmed COVID-19 individual, instead of the workplace[16]. Socio-demographic risk factors may differ based on the culture and geographical differences, and the availability of resources. The cross-transmission of SARS-CoV-2 among the household is well-established concept and persists even during the low-community transmission[17].

The current study also found a significantly higher proportion of the infected frontline HCWs were staying in shared accommodation. When comparing infected HCWs per month with average new cases in the community, an agreement was observed in the peaks of two trend charts (Figure 1). This pattern reveals a synchronization in the infection rate among the HCWs and the transmission rate of SARS-CoV-2 infection in the community. Hence, the HCWs are vulnerable to contracting the infection from their households and social contacts, especially with a higher rate of SARS-CoV-2 transmission in the community. Hospital leadership can utilize this valuable insight for workforce management and to develop strategies to mitigate the risk of exposure to HCWs. Theoretically, public transport can be another risk factor for transmission. However, as reported in the literature, the current study authors did not find any increased transmission risk with public transport[18].

Table 4 Attitude and perception of the infected healthcare workers, *n* (%)

Are you aware about appropriate personal protective equipment for the care of COVID-19 patients?	Yes: 99.3%; No: 0.7%
Have you ever been exposed to a COVID-19 patient without adequate PPE?	Yes: 43 (15); No: 243 (85)
There was always enough PPE in my workplace	Agree: 183 (64); Neutral: 36 (12.6); Disagree: 67 (23.4)
PPE availability and quality should be improved at my workplace	Agree: 85 (29.7); Neutral 49 (17.1); Disagree: 152 (53.2)
Proper precautions (face mask, hand hygiene, social distance) are most important tools to save you from SARS-CoV-2	Agree: 213 (74.4); Neutral: 12 (4.2); Disagree: 61 (21.3)
Vaccines for SARS-CoV-2 can reduce infection rate and can prevent severe disease and hospitalisation	Agree: 201 (70.2); Neutral: 27 (9.6); Disagree: 58 (20.2)

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; PPE: Personal protective equipment.

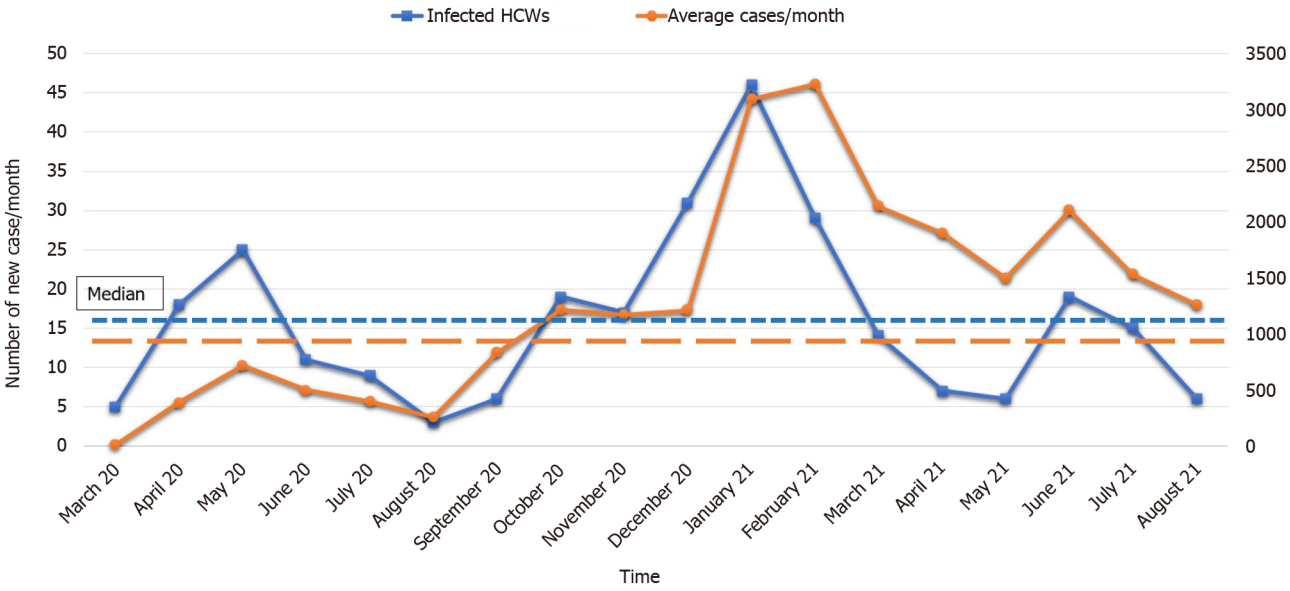

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Figure 1 Trend-chart showing the month-wise distribution of infected healthcare workers and new cases in the community. Infected healthcare workers (HCWs) are displayed in absolute numbers per month (orange color) and average cases of severe acute respiratory syndrome coronavirus 2 cases in the community (blue color). Median cases per month are displayed through dashed lines. There are three peaks observed in trend-line. The peaks coincided in the trend charts, representing an increased rate of infection among HCWs with high community transmission. HCWs: Healthcare workers.

According to a study conducted earlier, the vaccination of the HCWs effectively reduces the risk of severe disease and the transmission of SARS-CoV-2[19]. Advanced age (≥ 65 years), male sex, and other co-morbidities like diabetes mellitus, chronic respiratory disease, hypertension, chronic kidney disease, and cardiovascular disease are risk factors for severe illness and mortality[20]. COVID-19 vaccination is highly effective in reducing the progression and the severity of disease and intensive care unit (ICU) or hospital admission, especially in the elderly population and patients with co-morbidities[21]. Vaccination is an essential intervention for the HCWs to protect them from getting infected and severe illness that may require hospital or ICU admission. However, the effectiveness of the vaccine in reducing the risk of disease reduces considerably after six months of the last dose. So, a booster dose is recommended for the vulnerable population, including HCWs[19]. Vaccine hesitancy among the HCWs is a major issue in the successful implementation of the COVID-19 vaccination programme. Only 70.2% of the participants have agreed upon the efficacy of the COVID-19 vaccines. Other studies also found more vaccination hesitation among the previously infected people[22,23]. Hospital leadership and infection preventionist should address the issue of vaccine hesitancy strategically and through collaboration.

Strength and limitations

This is the first study to the best of the author's knowledge from the UAE or the countries in the Gulf Cooperation Council on risk profiling of RT-PCR-positive HCWs with COVID-19 using socio-

demographic factors. The study also evaluated the impact of COVID-19 vaccination on cross-transmission among the HCWs. The current study has a few limitations that are listed herewith. Firstly, the information on social contacts and households was collected through a cross-sectional survey. Hence, there exists a potential recall bias because of the time-gap between the period of infection and data collection. However, to avoid this bias, the data collected from the cross-sectional survey was validated through the human resource records maintained by the hospital.

There is missing data for about 17% of the eligible HCWs who did not participate in the cross-sectional survey due to reasons like resignation and immigration to other countries. Secondly, genomic sequencing was not used to confirm the phylogenetic linkage in infection among co-workers or the household. Thirdly, the small cohort size could have missed portraying the complete statistical correlation of various socio-demographic factors. Finally, the impact of the COVID-19 vaccination booster on transmission dynamics was not assessed.

CONCLUSION

The risk profiling of the HCWs, infected with SARS-CoV-2 from two tertiary care hospitals showed that the frontline HCWs had a significantly higher infection rate. Another significant risk factor was male sex. COVID-19 vaccination can effectively reduce the rate of SARS-CoV-2 transmission among HCWs.

ARTICLE HIGHLIGHTS

Research background

There is paucity of the research on the transmission dynamics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among the healthcare workers (HCWs) and their co-workers and household. The current study conducted a retrospective analysis of the infected HCWs to analyze the socio-demographic risk factors and characteristics of SARS-CoV-2 transmission among HCWs and their social contacts.

Research motivation

HCWs are vulnerable to SARS-CoV-2 infection during their work, and the potential risk of transmission of SARS-CoV-2 infection from the household and co-workers of HCWs is unclear. This study provides valuable insights for workforce management and helps formulate strategies to mitigate the risk of exposure to the HCWs.

Research objectives

The current study evaluated the risk factors of SARS-CoV-2 infection among HCWs and explored the potential of transmission of SARS-CoV-2 among the household and co-workers of infected HCWs.

Research methods

The health records of all infected HCWs between March 2020 and August 2021 were analysed. The information on the coronavirus disease 2019 (COVID-19) vaccination, household and co-workers of the infected HCWs was collected through a cross-sectional survey.

Research results

The cross-sectional analysis of health records of 346 reverse transcriptase polymerase chain reaction (RT-PCR)-positive HCWs showed that the risk of infection was significantly higher among frontline HCWs. Being male was a significant risk factor for SARS-CoV-2 infection. Among infected frontline staff, a significantly higher proportion were male, and were staying with their families in rented accommodation. COVID-19 vaccination was effective in reducing the infection rate among HCWs.

Research conclusions

Working at the frontline and being male are the significant risk factors for SARS-CoV-2 infection among the HCWs. COVID-19 vaccination is effective in reducing the infection rate among HCWs.

Research perspectives

Future research should explore the role of community transmission of SARS-CoV-2 in the infection of HCWs.

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FOOTNOTES

Author contributions: Nasa P, Modi P, Sebutel G, Upadhyay S participated in the acquisition, analysis, and interpretation of the data; Nasa P drafted the initial manuscript; Syed T, Modi P, Sebutel G, Puspha A, Upadhyay S revised the article critically for important intellectual content.

Institutional review board statement: The study was approved by the scientific and ethical committee of the NMC Healthcare and the Dubai Scientific Research Ethics Committee (Approval No. DSREC/09/2020_32).

Informed consent statement: All involved participants of the cross-sectional survey gave their informed consent (written) prior to study inclusion.

Conflict-of-interest statement: There are no conflicts of interest to report.

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LETTER TO THE EDITOR

Utility of cardiac bioenzymes in predicting cardiovascular outcomes in SARS-CoV-2

Ali Osman Gulmez, Sonay Aydin

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Abstract

The relationship between coronavirus disease-19 (COVID-19) and cardiovascular diseases has been an important issue. Therefore, cardiac biomarkers and cardiac imaging have an important place in the diagnostic phase. It is important to know the relationship of biomarkers in COVID-19 so that we can understand the diagnosis of the disease, the predicted course and results after diagnosis.

Key Words: Cardiac bioenzymes; Coronavirus disease - 19; Treatment; Diagnosis; Triple rule-out computed tomography angiography; Dual energy computed tomography

Core Tip: Recommends biomarkers, especially troponin, in patients with Coronavirus disease-19-associated myocarditis and other myocardial damage; however, they have proven that in addition to traditional biomarkers, new cardiac bioenzymes such as prepesin, copeptin also increase and significantly worsen the prognosis. Knowing this, evaluation together with other imaging methods is also important in diagnosis.

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TO THE EDITOR

We read with interest and attention the review written by Muthyala *et al*[1]. One of the main effects of the coronavirus disease 2019 (COVID-19) pandemic is on the cardiovascular system. Therefore, it is important to know and use cardiac biomarkers well, and to come to an advanced point in the diagnosis stage by combining them with cardiac imaging methods. Therefore, the authors discussed the importance of these biomarkers in COVID-19 in order to determine the ways to diagnose the disease, follow-up after diagnosis and treatment. Although biomarkers are important, we also mentioned them in our evaluation since it is important to evaluate them with imaging methods. We think that when we combine cardiac biomarkers and imaging methods, a very important point will be reached in the diagnosis.

Including troponin[2], which provides us with information about the prognosis in the diagnosis of cardiac acute coronary syndromes and myocardial damage, as well as Brain Natriuretic Peptide (BNP) [3] and pro-BNP, which gives us an advantage in the early detection of heart diseases and understanding the morbidity status of such diseases. Natriuretic peptides, especially natriuretic peptides, tend to be elevated and associated with poor prognosis in patients with heart disease, which is independently thought to be associated with COVID-19 even though the patients have no history of cardiac disease. In this review, the authors summarized the role of biomarkers in determining and diagnosing the extent of involvement of heart damage in people with COVID-19, as well as the permanent damage they may cause in the future. In the review, the researchers divided it into three main sections, considering the diagnosis, prognosis, and mortality in order to simplify the role of cardiac biomarkers in COVID-19 disease. These three sections are as follows: (1) The relationship between cardiac troponin and COVID-19-related myocardial disease; (2) The relationship between natriuretic peptides and COVID-19-related myocardial disease; and (3) The rest of the biomarkers are associated with myocardial disease.

Troponin consists of three main proteins in a complex structure[4]; Troponin C binds calcium and regulates the work of thin filaments during contraction[5]. Troponin T provides the connection of troponin in a complex with tropomyosin[6]. Troponin I acts as an inhibitory unit, and troponin C prevents contraction in the absence of calcium[7]. The amount of troponin that rises during myocardial injury has been observed to be higher among patients with COVID-19 who died compared to those who survived. In studies concentrating on this subject, a significant relationship has been shown between troponin and mortality with additional patient and hospital-related conditions, even in patients without comorbidities[8,9,10].

BNP is first proteolytically processed from its precursor proBNP to BNP. Afterwards, it is secreted from the heart as N-terminal proBNP (NT-proBNP), undivided proBNP and mature BNP and NT-proBNP in ventricular myocytes, and the amount of secretion increases in patients with heart failure [11]. In the review, it is concentrated that the main reason for the increase in natriuretic peptides in severe acute respiratory syndrome coronavirus 2 is some inflammatory processes that can lead to fulminant myocarditis. However, heart damage and hypoxia are thought to be some of the important causes of the increase in natriuretic peptides.

However, the cardiac markers mentioned in the review alone cannot rule out cardiovascular disease. Although it is supported by electrocardiogram (ECG), it may show atypical symptoms. Therefore, the differential diagnosis of acute chest pain after the new types of COVID-19 has become complicated. The viscosity increase due to COVID-19 hypoxia also causes damage to endothelial cells, resulting in increases in coagulation. In cases where biomarkers and ECG are insufficient at this stage, Triple rule-out computed tomography angiography (TRO CTA) provides us an advantage in examining the entire thoracic vascular system and detecting cardiovascular vascular diseases.

One of the important points of the new COVID-19 disease is that this disease has the potential to cause acute presentations. One of the most important of these tables is acute chest pain, which also includes respiratory tract diseases, which is the most common symptom of COVID-19. In these cases, one of the important causes of acute chest pain is diseases that affect the lung parenchyma or accompanying vascular pathologies in COVID-19 cases. In a study conducted in these cases, it is emphasized that TRO CTA is an important diagnostic method that is effective and does not require intervention to the patient in those who apply to the emergency department with sudden onset symptoms[12].

One of the important points apart from acute presentations is the long-term effects of COVID-19. In one study, persistent long-term COVID symptoms such as shortness of breath, chest pain, cough, and muscle weakness were proven to be associated with computed tomography (CT) severity values[13]. In this review, it is also emphasized that the relationship of CT with persistent symptoms yields better data than laboratory parameters. Knowing the relationship between CT severity and long-term COVID symptoms can also help to identify at-risk patients and establish follow-up programs to support these cases.

COVID-19 damages the myocardium by various mechanisms. The review focused on multiple viral infections causing sympathetic activation, direct viral invasion and proinflammatory cytokines inducing heart failure. The main reason for the increase in natriuretic peptides increased as a result of myocardial damage is thought to be due to interleukin (IL)-1β and similar proinflammatory cytokines. Magnetic

Resonance Imaging (MRI), which has an important place in the diagnosis of myocarditis, also has an important place in imaging in myocarditis formed in this way; however, Cardiac MRI has some disadvantages such as not being ubiquitous, high cost, claustrophobia, incompatibility with pacemaker and its application due to prostheses. In these cases, in a study conducted, Dual Energy CT (DECT) has proven to be significantly superior to MRI[14].

The authors recommend natriuretic peptides such as troponin and BNP in patients with myocarditis and other myocardial damage mentioned in the study; however, they proved that in addition to traditional biomarkers, new cardiac bioenzymes such as prepesin, soluble ST2 and copeptin also increase and cause marked worsening of prognosis. In addition to biochemical markers, imaging methods, especially CT, have an important place in the diagnosis of myocardial damage and comorbidities in COVID-19 patients. To give an example, DECT is used in practice as an important imaging method in the diagnosis of myocarditis-like conditions with myocardial damage[14]. TRO CTA is a frequently used imaging method in the detection of hypercoagulation, which we can give as an example of comorbidity conditions[12].

In summary, we have seen that there is a significant relationship between COVID-19 and cardiovascular system findings. After understanding this relationship, we learned that we should make the best use of the data we have at the point of diagnosis. Here, we know that we need to proceed to diagnosis by combining many cardiac biomarkers such as laboratory values such as BNP and pro-BNP with imaging methods such as ECG, CT, DECT and TRO CTA. In conclusion, we should make the best use of all available methods for diagnosis and treatment in order to reduce cardiovascular-related mortality and morbidity rates and improve prognosis in these patients.

FOOTNOTES

Author contributions: Aydin S and Gulmez AO conceived the study; Aydin S and Gulmez AO were responsible for designing, materials and supervision; Aydin S and Gulmez AO did the literature search, wrote the manuscript, and reviewed the manuscript critically; All authors have read and approved the final manuscript.

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