The Pathogenesis of Gastrointestinal, Hepatic, and Pancreatic Injury in Acute and Long Coronavirus Disease 2019 Infection

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KEYWORDS

• SARS-CoV-2 • Long COVID • Gastrointestinal • MAFLD • Insulin resistance

KEY POINTS

- Gastrointestinal (GI) and pancreatic tissues express high levels of angiotensin-converting enzyme-2 and are targeted during acute coronavirus disease 2019 (COVID-19) infection.
- A subset of patients with long COVID develops GI manifestations.
- Mechanisms underlying GI involvement in long COVID are complex and include viral persistence, mucosal and systemic immune dysregulation, microbial dysbiosis, insulin resistance, and metabolic abnormalities.
- Rigorous definitions and pathophysiology-based therapeutic approaches are needed to mitigate the morbidity associated with these disorders.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting disease, coronavirus disease 2019 (COVID-19), first emerged in Wuhan, China, in 2019 and became a worldwide pandemic within months. The manifestations of COVID-19 infection range from asymptomatic infection to severe disease and death. Although respiratory failure and systemic inflammatory response syndrome (SIRS) are the hallmarks of severe disease, COVID-19 is clearly a multisystem disorder with postacute sequelae. Rigorous research focused on understanding the acute and chronic illness associated with COVID-19 remains a priority.

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PATHOGENESIS OF ACUTE CORONAVIRUS DISEASE 2019 INFECTION

SARS-CoV-2 is a member of the Betacoronavirus genus,[1,2] which also includes severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). The virus is an enveloped virus with a positive-sense RNA-strand genome. The virion contains 4 main structural proteins—spike (S), envelope (E) and membrane (M) proteins in the viral membrane, with genomic RNA complexed with nucleocapsid (N) protein. Cellular entry is facilitated by interactions between the viral spike (S) glycoprotein and the host cell receptor, angiotensin-converting enzyme-2 (ACE2), leading to the fusion of viral and cellular membranes.[3] The transmembrane serine protease (TMPRSS2) is the main host cell protease, which cleaves the S protein of SARS-CoV-2 and facilitates viral entry into the cytoplasm of the host cell. Therefore, coexpression of ACE2 and TMPRSS2 is critical for host-cell entry by SARS-CoV-2. After entry, viral RNA is released and translated into viral polyproteins.[4] These polyproteins are cleaved by virus-encoded proteases to facilitate replication and produce full-length negative-strand RNA and subgenomic RNA. Subgenomic RNA is then translated into structural and accessory proteins and mature virions are exocytosed from the host cell.

The innate immune system serves as the first line of defense against SARS-CoV-2[5] by limiting viral entry, translation, replication, and assembly. Further, the innate immune system helps identify and remove infected cells, coordinates with and accelerates the development of adaptive immunity. The adaptive immune responses, driven by B cells and T cells,[6] are slower due to the intrinsic requirement of selecting and expanding virus-specific cells from the large pools of naïve cells. Viral Spike protein is targeted by SARS-CoV-2 neutralizing antibodies, with the receptor-binding domain of Spike being the target of greater than 90% of neutralizing antibodies. Further, SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells are directed against a range of viral antigens that are significantly associated with reduced disease severity.

Evolution of SARS-CoV-2 and emergence of new variants has raised concerns that these variants (variants of concern [VOC]) could increase pathogenesis by escaping antiviral immune responses.[7] SARS-CoV-2 can specifically evade the innate immune system by encoding for several proteins that disrupt the retinoic acid-inducible gene I-like receptors sensing pathways, as well as the induction, signaling, or effector functions of interferons (IFNs). Mutations found in VOCs primarily cluster in the receptor binding motif, resulting in increased binding to ACE2 and escape from neutralizing antibodies. Furthermore, mutations and deletions in the N-terminal domain can change the domain structure and may account for differences in the induction of neutralizing antibodies. Understanding the mechanisms that new variants use to escape the immune system and their relation to altered disease pathogenesis is an active area of research.

Acute COVID-19 usually lasts for 4 weeks from symptoms onset. However, in a subset of individuals, postacute sequelae of COVID-19 (PASC) or “long COVID” are observed, although the natural history of long COVID and the inciting causes are not well understood. This review is focused on understanding the manifestations and mechanisms of long COVID, particularly because they relate to the gastrointestinal (GI) tract.

Pathogenesis of “Long Coronavirus Disease”

Persistent, prolonged, and often debilitating sequelae are increasingly recognized in COVID-convalescent individuals[8] and are termed “long COVID,” “long-haul-COVID,” or PASC. Although the definitions of this syndrome are inconsistent,[9] the WHO definition of long COVID includes prior “probable or confirmed” SARS-CoV-2 infection, with

symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. However, the National Institute for Health and Care Excellence defines long COVID as a syndrome that develops during or after an infection consistent with COVID-19 continues for more than 12 weeks and is not explained by an alternative diagnosis.

The common manifestations of long COVID are systemic (fatigue and poor concentration), neuropsychiatric (sleep abnormalities, chronic headache, "brain fog," defects in memory, mood impairment, and pain syndromes), cardiac (palpitations, syncope, dysrhythmias, and postural symptoms), respiratory (dyspnea and cough), and GI (nausea, vomiting, anorexia, diarrhea, and/or abdominal pain).[8] Adopting accurate and consistent definitions of long COVID permits careful clinical evaluation of the symptoms, and distinguishes prolonged damage associated with acute illness from new symptoms that develop after the acute disease resolves.

Several hypotheses regarding the pathogenesis of long COVID have been proposed,[10] including the following: (1) delay in the resolution of infection and persistent inflammation, (2) persistence of virus or viral antigens in tissues, (3) triggering of autoimmunity, and (4) aberrant immune responses, including dysregulated cytokine production.

Among the studies that have defined the pathogenesis of long COVID, a prospective, case–control study of 31 patients with long COVID, matched with 31 convalescent individuals without long-COVID sequelae,[11] found elevated serum levels of proinflammatory cytokines (IFNβ, IFNλ1, IFNγ, CXCL9, CXCL10, IL-8, and soluble T cell immunoglobulin and mucin domain-containing protein 3 [Tim-3]) in both groups after 4 months of acute infection. However, at 8 months after infection, only the patients with long COVID had a persistent increase in levels of IFNβ and IFNλ1 in circulation and expansion of peripheral blood-associated $PD1^+$ or $TIM3^+CD8^+$ memory T cells, activated ($CD86^+CD38^+$) plasmacytoid dendritic cells, and $CD14^+CD16^+$ monocytes.[11] These data demonstrate that long COVID is associated with a sustained inflammatory response.

Long COVID was further studied longitudinally in a cohort of 309 patients with COVID-19 who were evaluated from the time of diagnosis to convalescence, 2 to 3 months postinfection.[12] Detailed multiomic investigation identified 4 parameters that anticipated the development of long COVID. These included type 2 diabetes mellitus, high initial SARS-CoV-2 viremia, reactivation of latent viruses (especially Epstein–Barr virus [EBV]), and the presence of specific autoantibodies during or preceding the acute stage of COVID-19 infection.[12] Notably, specific autoantibodies such as anti-IFNα2 were linked to inhibition of IFN-dependent B cell responses (evidenced by a negative correlation between anti-SARS-CoV-2 antibodies and anti-IFNα2 antibodies). Additionally, IFNα2 inhibition was linked to the upregulation of inflammatory cytokines that characterize long COVID. Furthermore, many aberrant immune cell populations were enriched in patients with long COVID. These included cytotoxic $CD4^+$ T cells, exhausted T cells and myeloid-derived suppressor cells.[12]

Another prospective, multicenter study of 215 individuals identified a distinct SARS-CoV-2-specific immunoglobulin signature during acute infection among those who subsequently developed long COVID.[13] This included reduced IgM and IgG3 titers during acute infection. Because IgM and, particularly, IgG3 secretion by B cells is induced by IFNs and antagonized by interleukin-4 (IL-4), this study suggested that the aberrant immunoglobulin signature associated with long COVID is related to reduced production of type I IFNs, resulting in a failure of antibody isotype switching.

In a recent cross-sectional study that included 101 individuals with long COVID, 41 convalescent individuals without long COVID (median times from acute disease of 432 days and 344 days, respectively) and 41 uninfected healthy controls, cellular

and soluble immune parameters were examined.[14] In this study, when compared with individuals without long COVID, those with long COVID had a significant increase in levels of nonclassical monocytes ($CD14^{low}CD16^{hi}$), activated B cells ($CD86^{hi}HLA\text{-}DR^{hi}$), double-negative B cells ($IgD^{-}CD27^{-}CD24^{-}CD38^{-}$ cells), and exhausted ($PD\text{-}1^{+}$/$Tim\text{-}3^{+}$) $CD4^{+}$ T cells and $CD8^{+}$ T cells. Additionally, long COVID individuals had higher titers of anti-EBV antibodies, although the overall seroprevalence of EBV in long COVID individuals was not different from healthy or convalescent controls. Further, and perhaps a striking observation was that long COVID individuals had a persistently decreased cortisol production more than a year after acute infection when compared with healthy or convalescent controls. This high-dimensional profiling of the peripheral blood supports the hypothesis that there are significant and persistent biological differences in patients who develop long COVID that include persistence of antigen, reactivation of latent herpesviruses, and chronic inflammation.

TARGETING OF THE GASTROINTESTINAL TRACT BY SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 DURING ACUTE CORONAVIRUS DISEASE 2019 INFECTION

GI symptoms including nausea, vomiting, anorexia, diarrhea, and/or abdominal pain are common extrapulmonary manifestations during acute COVID-19 infection.[15] The incidence of GI symptoms in patients with COVID-19 varies between different studies, ranging from 3% in the initial reports from Wuhan,[16] up to 61.3% in a multicenter cohort from the United States.[17] Based on a systematic review and meta-analysis of 47 studies and more than 10,000 patients, GI symptoms were observed in around 10% of patients with acute COVID-19.[18] An important clinical question is the association of GI symptoms with COVID-19 outcomes. To address this, we investigated a cohort of 634 patients with COVID-19 who were admitted to Mount Sinai Hospital. Patients presenting with GI symptoms had less severe disease than patients without GI symptoms ($P < .001$), and mortality was significantly lower in patients with GI symptoms (15.7%) than those without (31.0%; $P < .0001$).[19] These data were confirmed in an external validation cohort of 287 hospitalized patients from Milan, Italy,[19] and were consistent with 2 prior studies.[20,21] However, these findings contrast with early studies from Wuhan, China, where the presence of GI symptoms in patients with COVID-19 was associated with an unfavorable prognosis.[22,23] Possibly this discrepancy may arise from the inclusion of abnormal liver enzymes (which are associated with worse outcomes)[23] or iatrogenic confounders[22] in the Wuhan studies.

Robust and constitutive expression of ACE2, the receptor for SARS-CoV-2, on the brush border of small intestinal epithelium,[24] enables viral entry into intestinal cells. GI infection by SARS-CoV-2 is further supported by in vitro studies using human small intestinal organoids[25,26] and a high prevalence of viral shedding in stool, particularly after viral RNA negativity in respiratory specimens.[27] Endoscopic evaluation of the GI tract in patients with COVID-19 (in the acute, or immediate postacute stage of COVID-19) is usually unremarkable with a notably "normal" histological appearance of intestinal tissues, often with a scant neutrophilic infiltrate or mild increase in intraepithelial lymphocytes[19] in contrast to the dense inflammatory infiltrate that accompanies pulmonary infection with SARS-CoV-2. Further, detailed immunophenotyping of intestinal tissues in patients with COVID-19, reveals reduced frequencies of conventional dendritic cells ($CD206^{+}CD1c^{+}$ cDC2) and plasmacytoid dendritic cells with an increase in the frequency of effector T cells. Transcriptional signatures (using bulk RNAseq of intestinal biopsies) reveal a significant downregulation of pathways associated with inflammation and antigen presentation in the lamina propria with a

concomitant activation of antiviral response signaling genes in the epithelial compartment.[19] Further, patients with COVID-19 with GI symptoms have reduced levels of circulating inflammatory cytokines (including IL-6, IL-8, IL-17, and CCL28) compared with patients with COVID-19 without GI symptoms.[19] Altogether, these data suggest that although the GI tract can be infected by SARS-CoV-2, when compared with the lungs, there appears to be an attenuated inflammatory response in the intestines in the acute stage. Although speculative, this raises the possibility that a "less than sterilizing" intestinal immune response to SARS-CoV-2 may allow for viral persistence in GI tissues as detailed below.

GASTROINTESTINAL INVOLVEMENT IN LONG CORONAVIRUS DISEASE

GI manifestations are well reported in patients with long COVID, although their frequency is not clearly defined.[10] Long COVID–associated GI symptoms include—loss of appetite, nausea, weight loss, abdominal pain, heartburn, dysphagia, altered bowel motility, and irritable bowel syndrome (IBS).[10] In a prospective cohort of 1783 COVID-19 recovered individuals (with 749 responders to survey questionnaires), 220 patients (29%) self-reported GI symptoms at 6 months that included diarrhea (10%), constipation (11%), abdominal pain (9%), nausea and/or vomiting (7%), and heartburn (16%).[28] In another study of 73,435 users of the Veterans Health Administration, motility disorders (including constipation and diarrhea) and esophageal disorders (including dysphagia) were reported as postacute sequalae of acute COVID.[29]

Unique characteristics of the GI mucosal immune compartment may underlie the pathophysiology of long COVID that include viral persistence, aberrant immune activation in the GI tract, intestinal dysbiosis, and maladaptive neuro-immune interactions as detailed below.

Viral Persistence in the Gastrointestinal Tract

We first reported on the persistence of SARS-CoV-2 antigens in the GI tract after an average of 4 months (range 2.8–5.7 months) post-COVID-19 infection.[30] Intestinal enterocyte-associated SARS-CoV-2 N protein was detected in 5 out of 14 individuals while in 3 out of the 14 participants, polymerase chain reaction (PCR) amplicons were sequence verified as SARS-CoV-2.[30] Viral detection in GI tissues, which was patchy and sporadic, likely truly underestimate viral persistence. Although none of the patients in the initial study suffered from long COVID, the data provided proof of the principle that SARS-CoV-2 can potentially persist in specific tissues in a manner consistent with the persistence of other nonretroviral RNA viruses. Goh and colleagues[31] established the presence of residual virus in GI tissue (appendix) and non-GI tissues (skin, and breast) in 2 patients who exhibited long COVID symptoms 163 and 426 days after symptom onset, respectively. In another cohort of 46 patients with inflammatory bowel disease, patients who tested negative for mucosal SARS-CoV-2 RNA (30%) did not experience persistent symptoms, whereas in patients who tested positive for SARS-CoV-2 RNA (70%), a majority (65.5%) experienced long COVID symptoms.[32] GI involvement in long COVID is associated with unique T cell clonal and transcriptome dynamics that include a significant enrichment of the cytotoxic T cells associated with bystander activation of CMV-specific cells.[12] Ongoing work in our group also identifies persistent lymphoid and myeloid cell abnormalities in the GI tract up to 10 months after initial infection.[33] Altogether, emerging data provide evidence of protracted viral antigen persistence and immune cell abnormalities in GI tissues. However, to-date, intact virions have not been cultured from patients with long COVID, and there is no evidence yet of viral evolution in intestinal tissues.

Microbial Dysbiosis Associated with Long Coronavirus Disease

Studies have also begun to dissect the association between the intestinal microbiome and long COVID. The composition of the fecal microbiome was examined using shotgun metagenomic sequencing in a prospective cohort of 106 patients who were followed from admission up to 6 months postinfection.[34] Although this study was skewed by a high representation of individuals with moderate-to-severe COVID-19 (73.5%) and a high prevalence of long COVID–associated symptoms (73.5%), reduced microbial diversity and higher levels of *Ruminococcus gnavus*, *Bacteroides vulgatus*, and lower levels of *Faecalibacterium prausnitzii* were associated with long COVID in this study.[34]

Alterations in the Gut–Brain Axis in Long Coronavirus Disease

In a survey of patients hospitalized with COVID-19 and followed-up for at least 6 months, persistent GI symptoms meeting the Rome IV criteria were found in 39% (44 out of 112) of patients.[35] A validated survey to determine the severity of IBS symptoms (the IBS severity scoring system IBS-SSS) reported a significant increase in severe IBS after COVID-19. Given the high frequency of motility-related disorders associated with GI long COVID, postinfectious neuro-immune related disorders should be considered in disease pathogenesis. Possible mechanisms involve microbial dysbiosis, increased intestinal permeability, and low-grade intestinal immune activation. Small animal model studies demonstrate that cross talk among gut-innervating specialized sensory neurons (nociceptors), microbes, and intestinal epithelial cells regulate the mucosal host defense.[36] Further, muscularis propria-resident macrophages, in close apposition with enteric neurons cell bodies, acquire tissue-protective phenotypes that prevent neuronal loss after infection.[37] Although there are no data at present, we anticipate that examination of intestinal neuro-immune cross talk in patients with long COVID will be illuminative.

HEPATIC INVOLVEMENT BY SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2

The mechanisms of hepatic dysfunction in long COVID patients are poorly understood. A subset of patients may manifest with abnormal liver function tests 6 months after COVID-19 resolution. In most such cases, patients receive the diagnosis of metabolic-associated fatty liver disease (MAFLD). However, it is unclear whether MAFLD is coincidental, or a consequence of persistent inflammation seen in some COVID-19 patients. A few other hypothesized mechanisms include SARS-CoV-2-induced direct injury or persistence within the liver, dysregulated gut–liver axis, or chronic and systemic inflammation.

Although hepatocytes exhibit a lower expression of ACE2 than enterocytes, scavenger receptor class B type 1, posited as a potential interactor with SARS-CoV-2, is highly expressed in the liver.[38] A study of hepatic autopsies demonstrated the presence of SARS-CoV-2 RNA and S proteins in liver tissue by reverse transcription-PCR, immunofluorescence, and confocal microscopy.[39] Furthermore, transcriptomic and proteomic data suggest similarities between infection with SARS-CoV-2 and known hepatotropic viruses such as HBV, HCV, and HIV.[39] Nonetheless, there are no data at present to suggest that SARS-CoV-2 persists in the liver or is directly causative of MAFLD.

The gut–liver axis serves as a bidirectional conduit that enables a complex regulatory control of both systems. As detailed previously, a subset of patients manifest with protracted shedding of SARS-CoV-2 RNA in the stool, beyond acute infection.[27] Persistence of viral antigens in the GI tract can potentially alter intestinal permeability,

exposing the liver to luminal microflora, and accelerating hepatic injury due to the ensuing inflammatory responses. Furthermore, microbial dysbiosis post-COVID-19 could potentially affect not only the GI system but the gut–liver axis as well.[40,41] Notably, patients with long COVID when compared with non–long COVID convalescent individuals have a depletion of homeostatic, butyrate-producing bacteria and depletion of short-chain fatty acids.[42,43] Such perturbations are potentially associated with the establishment of a proinflammatory milieu in the liver, as demonstrated by elevated levels of proinflammatory cytokines including IFN-α, IFN-γ, IL-1β, IL-6, and TNF-α,[11,44,45] which can lead to MAFLD over time.[46] Additionally, dysregulation of oxidative and fatty acid metabolic pathways in patients with COVID-19,[47,48] and the resulting metabolic stress may result in hepatocyte apoptosis, lipid accumulation, and ultimately MAFLD.[44,49]

PANCREATIC INVOLVEMENT BY SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2

During acute COVID-19 infection, both endocrine and exocrine pancreatic dysfunction is described, characterized by new-onset diabetes and persistent hyperglycemia. It is plausible that patients with long COVID may develop new-onset diabetes through mechanisms that include direct cytotoxicity or pancreatic tropism, chronic inflammation, or both.

Pancreatic tissues express ACE2 and TMPRSS2 in ductal and β-islet cells at levels that are comparable to lung tissues.[50] In vitro studies utilizing induced pluripotent stem cell (iPSC)-derived pancreatic cultures as well as postmortem tissues demonstrate SARS-CoV-2 in pancreatic endocrine and exocrine cells and increased the expression of some pancreatic ductal stress response genes.[51,52] It was further suggested that β-cell infection could contribute to metabolic dysregulation observed in patients with COVID-19.[52] Detailed analysis of pancreatic autopsy tissue from patients with COVID-19 using immunofluorescence, immunohistochemistry, RNA scope, and electron microscopy reveals SARS-CoV-2 viral infiltration of beta-cells.[53,54] Notably, viral RNA within the pancreas, was detected in cells with weaker expression of ACE2 but a high expression of DPP4.[53] Moreover, SARS-CoV-2–induced local inflammation was associated with islet cell apoptosis.[53] In addition to direct cytotoxicity, β cell dysfunction may be attributed to the proinflammatory milieu associated with long COVID.

Altogether, based on existing data, both direct cytotoxicity of SARS-CoV-2, indirect inflammatory response within pancreatic tissue and the overall inflammatory milieu can lead to long-term pancreatic dysfunction in patients with long COVID.

SUMMARY

Gastrointestinal involvement is a recognized manifestation of long COVID. Underlying mechanisms are complex and may include viral persistence, immune dysregulation, reactivation of latent viruses, microbial dysbiosis, metabolic stress, and insulin resistance. Prospective studies with clearly defined patient populations and uniform definitions of the long COVID syndrome are required to better define the pathophysiology and to enable much needed therapeutic trials for this syndrome.

DISCLOSURE

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CLINICS CARE POINTS

- GI and pancreatic tissues are targeted during acute COVID-19 infection due to high levels of expression of ACE-2 in the physiological state.
- Common GI manifestations during acute COVID-19 include diarrhea, nausea, vomiting and abdominal pain.
- The common GI manifestations during long COVID are loss of appetite, nausea, weight loss, abdominal pain, heartburn, dysphagia, altered bowel motility, and irritable bowel syndrome.
- Several hypotheses regarding the pathogenesis of long COVID have been proposed. These include a) delay in the resolution of infection and persistent inflammation; b) persistence of virus or viral antigens in tissues; c) triggering of autoimmunity; and d) aberrant immune responses, including dysregulated cytokine production.
- A subset of patients who recover from acute COVID continue to demonstrate abnormal liver function tests up to 6 months post-infection that are related to metabolic associated fatty liver disease (MAFLD).
- Rigorous case definitions, longitudinal patient follow up and therapeutic clinical trials are urgently needed in patients with long COVID.

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