

The Pancreas in Coronavirus Disease 2019 Infection



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KEYWORDS

- Acute pancreatitis • COVID-19 • SARS-CoV-2 • Pancreatic cancer
- Chronic pancreatitis

KEY POINTS

- Many similarities between severe acute respiratory syndrome coronavirus-2 infection and acute pancreatitis (AP) are described but there is still a paucity of evidence to establish coronavirus disease 2019 (COVID-19) as a cause of AP.
- Patients with both COVID-19 and AP should be carefully managed because evidence indicates they may have a worse outcome.
- Careful attention to etiologic workup, patients comorbidities and chronic medications, disease management and diagnosis, and publishing guidelines should guide future case reports.
- COVID-19 vaccination has indisputable advantages but a few cases of AP have been reported after vaccination, which should alert and turn physicians to abdominal pain development after inoculation.
- Pancreas cancer diagnosis and management have been deeply influenced by the pandemic. Expert consensus and international and local guidelines should be implemented to allow safe management pathways to be resumed and improved.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for the pandemic of coronavirus disease 2019 (COVID-19) that has caused more than 600 million infections and 6.5 million deaths worldwide, involving more than 200 countries.¹

Initially considered a respiratory disease, the gastrointestinal tract has been described as playing a key role in the route of infection, clinical manifestations, and disease outcomes.² Pancreatic involvement was also found and several cases of pancreatic enzyme elevation and acute pancreatitis (AP) have been reported. However,

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the available data are difficult to interpret, and COVID-19 has not been definitively associated with AP, leaving several questions open.³

In this review, we aim to examine mechanisms of pancreatic involvement by SARS-CoV-2, the link between COVID-19 and AP, the influence of COVID-19 on chronic pancreatitis (CP), and the impact of COVID-19 on pancreatic cancer treatment, prognosis, and pancreatic surgery.

MATERIALS AND METHODS

A review of the literature was conducted using PubMed and EMBASE databases on September 26, 2022, for publications on COVID-19 and acute and CP and pancreatic cancer. A grey literature search using the same keywords was performed using Google Scholar to increase the search sensitivity. Articles on pediatric patients and pregnant women were excluded. References of eligible articles were also screened for additional articles. The literature search was restricted to articles published in English.

MECHANISMS OF PANCREATIC INJURY

Several studies have examined possible mechanisms of pancreatic injury by SARS-CoV-2.

SARS-CoV-2 enters human cells through angiotensin converting enzyme (ACE2) receptors, with transmembrane serine protease 2 (TMPRSS2) priming, which are highly expressed in human gastrointestinal cells.⁴ After viral entry, virus-specific RNA and proteins are synthesized in the cytoplasm of host cells to assemble new virions, which are then released to the gastrointestinal tract and detected in stool, confirming fecal-oral transmission.⁴

ACE2 is also highly expressed in pancreatic ductal, acinar, and islet cells,⁵ and the virus could thereby spread from the duodenal epithelium to the pancreatic cells. Furthermore, SARS-CoV-2 has been associated with endotheliitis and microischemic disease, which could occur in the pancreas.⁶

Histopathological studies in patients who died from severe COVID-19 infection report findings of pancreatitis and of SARS-CoV-2 identified in pancreatic pseudocyst fluid samples in patients who did not develop AP, showing SARS-CoV-2 tropism for pancreatic cells.⁷⁻⁹

SARS-CoV-2 has been reported to result in insulin deficiency and the development of type 1 diabetes mellitus.¹⁰ Although an increase of type 1 diabetes mellitus was observed in children, it is still unknown whether β cell injury is permanent or transient.^{10,11} Long-term results of the COVIDPAN study did not show an increased frequency of long-term diabetes.¹² In patients already diagnosed with diabetes, SARS-CoV-2 induced β cell dysfunction may cause an uncontrolled hyperglycemic state, which in turn may contribute to COVID-19 increased severity and mortality.^{10,13} Derangements of Na^+/H^+ exchange and lactate pathway are other potential mechanisms of glucose metabolism dysregulation from SARS-CoV-2 infection.¹⁴

A broad-spectrum of proinflammatory cytokines, including interleukin-2 (IL-2), IL-6, IL-8, IL-10, CXCL12, interferon (IFN)- γ , and tumor-necrosis factor- α , are released during COVID-19 infection, which may result from SARS-CoV-2 binding to ACE2 receptors in pancreatic cells^{15,16} but can also cause direct damage to surrounding dendritic cells and naïve T-cell activation in genetically predisposed individuals.¹⁷ It is also hypothesized that pancreatic lipase increases lipolysis and plasma levels of unsaturated fatty acids, which can in turn damage mitochondria and contribute to proinflammatory cytokine release.^{18,19} In both COVID-19 and AP, the cytokine storm is responsible for the disease severity, specifically elevated IL-6 levels, which are related to the

development of the acute respiratory distress syndrome and cause increased mortality in AP.^{20,21} Moreover, immune-response pathways are severely impacted by antibody production during SARS-CoV-2 infection, which may potentially cause increased IL-6 production.²² The cytokine storm is also directly involved in the coagulation cascade deregulation, which may in turn increase AP severity.²³

Several drugs used in the treatment of COVID-19, including corticosteroids, azithromycin, remdesivir, lopinavir/ritonavir, and IFN- β , have been implicated in the development of AP and hyperglycemia.^{13,24–27} Nevertheless, prednisolone is recommended for the treatment of specific preexisting conditions in patients with COVID-19, including cases of autoimmune AP.²⁸

Acute Pancreatitis and Coronavirus Disease 2019

AP seems an infrequent complication of COVID-19 and large retrospective studies found no increased incidence of AP during the pandemic.^{29–31} In fact, some centers have reported a decreased number of admissions for AP, probably due to patient reluctance to present to the emergency department during the pandemic but also because of reluctance of emergency room physicians to admit patients with mild AP.^{32,33} However, idiopathic AP was diagnosed in a greater proportion of patients with COVID-19, implicating SARS-CoV-2 in a causative role.^{29,34}

The diagnosis of AP should rely on the Atlanta criteria, and isolated elevations of amylase and lipase should not be misdiagnosed as AP.³⁵ In fact, SARS-CoV-2 can directly cause increased amylase and/or lipase levels and can also cause several complications that can increase the levels of these enzymes, including renal failure, acidosis, and diabetes. Up to 23% of patients may exhibit increased amylase levels but only a minority has AP according to the Atlanta Criteria.^{36–38} High lipasemia without AP can be detected in up to one-third of patients with COVID-19.^{39–41} Many case reports and case series have been published linking COVID-19 to AP development. However, most reports have a paucity of clinical information and a lack of adherence to CARE guidelines on publishing. Moreover, the temporal gap between COVID-19 diagnosis and AP is very heterogeneous making it difficult to establish a causal link between these entities in some cases. Complete etiological workup according to current evidence, including MRI and endoscopic ultrasonography, was pursued in a minority of patients, rendering the attribution of SARS-CoV-2 as the causative agent of AP doubtful in some cases.⁴² COVID-19 also causes immune dysregulation that may favor other infections, including cytomegalovirus (CMV), which in turn could cause AP.⁴³

Multivariate regression analysis revealed that elevated amylase and lipase levels were significantly associated with the severity of COVID-19, ICU admission, and mortality in hospitalized patients with COVID-19.^{36–38,44,45} Moreover, in patients without AP, elevations of pancreatic enzymes may be indicators of overall disease severity and poor prognostic indicators.^{46–50} Lipase/lymphocyte ratio was also found to be a predictor of mortality in AP patients with COVID-19.⁵¹ Single-cell sequencing data have identified a subgroup of neutrophils with high expression of IFN and a proinflammatory phenotype in COVID-19, which may be involved in AP severity.⁵² A low T-cell count has also been suggested as a surrogate for poor clinical outcomes.⁵³

Imaging findings suggestive of AP, including peripancreatic stranding and fluid collections, were more frequent in patients with COVID-19 and considering with elevations of pancreatic enzymes may aid in the diagnosis of AP, specifically in severe cases, when patients are frequently intubated.⁵⁴ However, computerized tomography of the abdomen is not strictly indicated in patients with elevated pancreatic enzymes levels because most frequently elevated amylase levels may be a nonspecific manifestation of shock/critical illness.⁵⁵

The temporal relation between AP and COVID-19 infection is very variable. AP may be more severe in patients with COVID-19 but not necessarily linked to the SARS-CoV-2 viral load, as suggested by the COVIDPAN study.³

Several studies found that patients with COVID-19 infection had significantly AP mortality^{32,56–60} and significantly increased the risk of severe AP,^{56,58,61} necrotizing AP,⁵⁶ ICU admission,^{32,57,60,61} need for mechanical ventilation²⁹ and longer length of hospital stay,^{29,56–58,62} compared with COVID-negative patients. Thus, AP may have a poor prognosis in patients with COVID-19. However, patients with previous inflammatory insults to the pancreas were found at greater risk of severe COVID-19 infection and mortality.⁶³

PANCREATITIS AFTER CORONAVIRUS DISEASE 2019 VACCINATION

The benefits of COVID-19 vaccination are indisputable. Only 2 cases of AP were reported in almost 38,000 patients during a phase 2/3 clinical trial of COVID-19 mRNA vaccine.⁶⁴ However, physicians should be aware of emerging side-effects, including severe abdominal pain after vaccination, which could indicate AP. The exact mechanisms of vaccine-induced AP are unclear but may be related to molecular mimicry. To our knowledge, only 6 cases of AP attributed to COVID-19 vaccination have been published.^{65–70}

Alcohol-Induced Acute Pancreatitis During Coronavirus Disease 2019 Outbreak

COVID-19 lockdowns dramatically influenced the population's social behavior. Several studies have shown an increase in alcohol consumption in the general population during COVID-19 lockdowns. An increase in hospital admissions for alcohol-induced AP has been observed in some hospitals during these periods, which have decreased after the restrictions were eased.^{71,72} However, this "shadow pandemic" of alcohol-related illnesses was not observed at all centers and all locations.³³

Chronic Pancreatitis and Coronavirus Disease 2019

There is a paucity of data about CP during the pandemic. Most cases have an attributable cause, thus making it difficult to link SARS-CoV-2 to either an aggravation of an existing CP or a new diagnosis of CP.

Recommendations on CP surgery have been made. A large international survey on pancreatic surgery agreed that CP surgery should be postponed, unless the patient is experiencing life-threatening complications.⁷³

Pancreas Cancer and Pancreatic Surgery During the Pandemic

The pandemic has deeply affected the diagnostic, management, and referral pathways of pancreatic cancer worldwide, with significant geographic variability,⁷⁴ including suspension of patient visits, imaging and endoscopic examinations, and delays and changes of elective cancer therapies and surgeries. These changes inevitably affect short-term and long-term patient care and prognosis and possibly decrease overall survival, although the specific influence on patients' outcomes is still unknown.^{75–83} In Italy, a reduction of 9.9% in new diagnosis of pancreatic cancer in 2020 compared with 2019 was reported.⁸⁴ More patients presented with more advanced pancreatic cancers in 2020 compared with 2019,^{80,81} and the pandemic caused considerable emotional and social distress among these patients, suggesting the need for a psychological support network.^{85,86} A third-level referral center in Italy recorded a 20% reduction in pancreatic resections during 2020 and a global survey from 267 centers in 37 countries reported a reduction in weekly pancreatic resections

from 3 to 1.^{73,87} Efforts should be made to reschedule pancreatic cancer surveillance programs and improve the staging and workup pathways to improve oncological outcomes.^{88,89} In a large multicenter prospective cohort study on pancreas and liver surgery outcomes during the pandemic, patients without SARS-CoV-2 infection had acceptable morbidity and mortality, highlighting the need to protect patients and continue to evaluate them for pancreatic cancer surgery.⁹⁰

Moreover, patients diagnosed with cancer require frequent hospital visits. They were found to have a 2-fold increase of COVID-19 infection, as compared with the general population.⁹¹ Immunosuppression as a cancer treatment effect, elevated cytokine levels, altered expression of receptors for SARS-CoV-2, and a prothrombotic state in patients with various cancers may exacerbate the effects of COVID-19. SARS-CoV-2 infection was associated with a significant increase in perioperative morbidity and mortality.⁹⁰

The optimal timing for surgery for pancreatic cancer is controversial, and no published guidelines exist on the timing for surgery for patients undergoing primary resection. The National Comprehensive Cancer Network (NCCN) guidelines recommend surgery at 4 to 8 weeks after completing neoadjuvant therapy.⁹² Based on the finding that no differences in mortality were found among stage I patients with pancreatic adenocarcinoma who received neoadjuvant and adjuvant therapy, the Society of Surgical Oncology recommended the administration of neoadjuvant therapy to all patients with resectable pancreatic cancer. Other recommendations included the extension of neoadjuvant therapy or radiation therapy.^{93,94}

The American College of Surgeons proposed an Elective Case Triage Guidelines for Surgical Care and categorized the growing severity of the COVID-19 pandemic in hospitals into 3 phases based on the availability of medical resources. Subsequently, a specific tier system for pancreatic surgery was proposed to guide pancreatic surgery for different pancreatic cancers according to patients' comorbidities, tumor malignant potential, and COVID-19 phase.⁹⁵ The European Society for Medical Oncology also developed specific guidelines for pancreatic cancer, defining priority grades for outpatient visits, imaging examinations, image-guided surgical procedures, and medical therapies to ensure the continuity of the oncological treatments during the pandemic.⁹⁶ An international survey on pancreatic surgery during COVID-19 also reached consensus on 13 statements and moderate agreement on 5 statements to guide pancreatic surgery.⁷³ National societies and expert centers developed consensus statements and analyzed the impact of COVID-19 on pancreas surgery to ensure optimal resource utilization and define treatment prioritization.^{97–102}

Recommendations for the prophylaxis of venous thromboembolism (VTE) and for the treatment of established VTE for patients with cancer are similar, regardless of whether they have COVID-19. As such, patients with cancer and COVID-19 should be assessed for VTE risk similar to any other patient. Pharmacological prophylaxis should be given in the same dose and with the same anticoagulant but primary prophylaxis of VTE is not recommended in ambulatory patients with COVID-19 with cancer.¹⁰³

New technologies, including telemedicine, have a role in the management of pancreatic cancer during the COVID-19 pandemic, and may gain increasing relevance in the future.¹⁰⁴

SUMMARY

SARS-CoV-2 infection and AP share several pathophysiologic similarities but there is still a paucity of evidence to establish COVID-19 as a cause of AP. Complete etiological workup and attention to patients' comorbidities, chronic medications,

and social habits, along with rigorous publishing guidelines, should guide future case reports.

COVID-19 also caused major challenges to pancreas cancer diagnosis and management, interrupting established management pathways. Several international and national consensus should be implemented as soon as possible to resume cancer treatments, including surgery, and minimize the negative pandemic effect on patient outcomes.

CLINICS CARE POINTS

- SARS-CoV-2 can cause pancreatic injury by several mechanisms, but it is yet to be established as a cause of AP.
- Etiologic workup is of major importance in establishing AP cause, especially in COVID-19 positive patients.
- International and national guidelines and norms should be put in practice to minimize the effects of the pandemic in pancreatic cancer diagnosis and management.

DISCLOSURE

The authors have nothing to disclose.

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