

# Role of the SARS-COV2 infection in the evolution of acute pancreatitis (Review)

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**Abstract.** Acute pancreatitis is characterized as an inflammatory illness that is life-threatening and causes necrosis as well as simple edema when pancreatic enzymes are activated intraglandularly. It is not known whether severe acute respiratory syndrome coronavirus 2 causes acute pancreatitis. Patients with acute pancreatitis who test positive for coronavirus disease 2019 (COVID-19) frequently have biliary or alcoholic causes. It is unclear how common acute pancreatitis is in patients with COVID-19. By contrast with patients without COVID-19, however, COVID-19-positive patients with acute pancreatitis have a higher mortality as well as a higher risk of necrosis and admission to an intensive care unit. The most common cause of mortality in COVID-19-positive individuals with concurrent severe pancreatitis is acute respiratory distress syndrome. The present study discussed research on the link between COVID-19 infection and acute pancreatitis.

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## 1. Introduction

Worldwide, coronavirus disease 2019 (COVID-19) and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread quickly from China. With high rates of infection, hospitalization, morbidity and mortality observed globally due to the COVID-19 pandemic, it has had a notable impact on public health (1-3). In addition to causing respiratory disease, COVID-19 leads to organ damage and multi-organ failure as a result of damage to the lung, heart, kidney and other organs (4).

COVID-19 has a strong tropism for gastrointestinal tract (5,6) However, the incidence of the digestive system being implicated ranges from 3 to 79% (7-9). COVID-19 infection may produce acute pancreatitis (AP) or exacerbated inflammatory response, which raises the risk of organ failure (10,11). AP is a common emergency condition and severe AP (SAP) affects 20-30% of patients diagnosed with AP (12). The mortality rate for SAP, a condition that poses a threat to life, ranged from 15 to 30% in a Dutch study (13). SARS-CoV-2 is linked to pancreatic enzyme increase and cases of AP, however the exact processes causing pancreatic injury are not known. In COVID-19, pancreatic damage rarely occurs. Inflammation that starts in the glandular parenchyma and spreads to the surrounding tissue as a result of AP damages or destroys the acinar component (14-17).

A small number of patients with COVID-19 exhibit only gastrointestinal symptoms, without a clear cause. However, COVID-19-induced acute pancreatic involvement is serious

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and can progress quickly. To provide appropriate treatment, close observation of clinical signs and paraclinical (laboratory and imagistic) investigations at admission are required. World Health Organisation only recently released statistics that estimate the number of COVID-related deaths, whether they are direct or indirect (2). This excess mortality includes both individuals who died and those who died from COVID without a diagnosis. The objective of the present review was to describe the association between AP and SARS-COV2 infection and assess whether COVID-19 can influence the prognosis of patients with AP.

## 2. Materials and methods

The current review conducted a literature search using 'acute pancreatitis' in combination with 'SARS-COV2 infection' or 'COVID infection' between February 2020 and January 2023 in the Pubmed and Scopus databases (18,19). The inclusion were criteria as follows: Relevant articles and reviews regarding the role of SARS-COV2 infection in the development of AP. Exclusion criteria were as follows: Studies that were not written in English, letters to the editor, speeches made at conferences, editorials, comments and publications that were not freely accessible.

## 3. COVID-19 and the pancreas

The symptoms of patients with COVID-19 infection are predominantly respiratory, with less frequent gastrointestinal symptoms (20-22). A meta-analysis of 60 studies that included 4,243 patients with COVID-19 showed a cumulative incidence of 17.6% for gastrointestinal symptoms, which included anorexia (26.8%), diarrhoea (12.5%), nausea/vomiting (10.2%) and abdominal pain/discomfort (9.2%) (8).

Patients with gastrointestinal symptoms who test positive for COVID-19 are more likely to develop severe respiratory distress and pancreatic injury, with a poorer prognosis (23).

With emergence of novel variants of COVID-19 and evidence obtained regarding the presentation of patients with COVID-19 infection, novel potential target organs have been identified based on expression of the angiotensin-converting enzyme 2 (ACE2) receptor that serves as the entry point into the cell for the virus (24). Xiao *et al* (21) found evidence of gastrointestinal infection with SARS-CoV-2 by detecting RNA and intracellular staining of the ACE2 receptor and viral nucleocapsid protein in gastric, duodenal and rectal epithelia. Studies using electron microscopy on tissue obtained from biopsies and/or autopsies have shown that the virus replicates highly in both small and large intestine (5,23-26). Patients with COVID-19 have viral RNA in their stools (27-31), which confirms the release of infectious virions in the gastrointestinal tract. For COVID-19 infection, fecal-oral transmission has been confirmed (32). In addition to being highly expressed in pericytes of the pancreatic microvasculature, ACE2 is expressed in human pancreatic cells and islets (5,33,34). Abnormal Laboratory results suggesting pancreatic injury have been detected in 8.0-17.5% of acute pancreatitis patients, with 7.0% showing substantial pancreatic alterations on computed tomography (35,36). It is currently unknown what causes pancreatic injury in patients with SARS-CoV-2.

Pharmaceutical drugs consumed prior to hospitalization as well as pancreatic ACE2 expression may be involved (37). In COVID-19, patients may exhibit elevated amylase levels but not all of these patients have AP. Stephens *et al* (38) showed that although a significant population of critically ill patients with COVID-19 exhibit elevated serum amylase concentration, only 1.7% of patients had a confirmed diagnosis of AP and the serum amylase levels did not influence mortality. There may be several causes of elevated serum amylase levels, including generalized intestinal inflammation or impaired renal excretion (39). Elevated serum amylase in patients with COVID-19 is not frequently caused by AP or clinical damage to the pancreas but may be a non-specific manifestation of COVID-19 or sepsis.

## 4. AP in COVID 19-positive patients

It is uncommon for COVID-19-positive patients to also have SAP. Only 10% of COVID-19-positive patients experience only stomach symptoms (40); typically, these patients experience the most severe COVID-19 infection. Additionally, it has not been proven that the COVID-19 pandemic saw a rise in the frequency of AP (41). It is not known whether SARS-CoV-2 causes AP. Most cases of AP in COVID-19-positive patients are idiopathic (42) and there is insufficient proof that COVID-19 can exacerbate AP or worsen its outcome. According to the COVIDPAN study, patients with COVID-19 and AP have more severe symptoms than COVID-19-negative patients (23).

Patients with AP who are positive for COVID-19 present with more severe cases of AP and higher risk of necrosis, admission to the intensive care unit (ICU), persistent organ failure and a requirement for mechanical ventilation. COVID-19-positive patients have a statistically greater 30-day overall mortality from AP (14.7%) than COVID-19-negative patients (2.6%) (23). Furthermore, SARS-CoV-2-positive patients have a higher likelihood of undergoing necrosectomy (5.0 vs. 1.3% in the control group). Inamdar *et al* (42) concluded from retrospective cohort analysis that pancreatitis should be considered a gastrointestinal manifestation of COVID-19. In 48,012 hospitalized patients, 189 cases of acute pancreatitis (0.39%) were reported by Inamdar *et al* (42). The rate of AP among those who are hospitalized for COVID-19 is 0.27%, with 32 (17%) of 189 patients being COVID-19-positive (42). Among positive patients, idiopathic AP was more prevalent (69%) than in COVID-19 negative individuals (21%). According to Wang *et al* (43), 17% of 52 patients with COVID-19 showed pancreatic damage, indicated by an aberrant rise in serum levels of amylase and lipase. According to Stephens *et al* (38), patients with COVID-19 do not always have an AP-related amylase serum peak. Only 1.7% of the study population fulfilled the updated Atlanta criteria (14) for diagnosis of AP, despite enrolling 234 individuals, 158 of whom had serum amylase levels three times higher than the normal upper limit (38).

In 121 patients with COVID-19, Liu *et al* (10) found that patients with severe COVID-19 have considerably increased odds of developing pancreatitis. Direct cytopathic action of COVID-19 may cause pancreas injury. Additionally, in the clinical condition systemic inflammatory response syndrome, the excessive immune response with a subsequent cytokine

storm and endothelial damage generated by COVID-19 may be the origin of pancreas injury (10).

AP in COVID-19 may be identified and reported concurrently with the identification of SARS-CoV-2 or several days after the first identification. Additionally, patients may have AP symptoms only yet test positive for COVID-19 infection. Abdominal discomfort, fever, and dyspnoea are the three symptoms that patients with COVID-19-related AP present with most frequently. In patients with COVID-19, the course of AP is typically mild. Pneumonia is a prevalent factor in COVID-19 prognosis (10). Certain individuals experience AP following hospitalization for SARS-CoV-2 infection. It is possible that AP is caused by COVID-19 treatment, such as steroids, remdesivir, or other pharmacological medicines (44,45). AP may coexist with COVID-19 without being a result of SARS-CoV-2 infection.

Patients with AP with concurrent COVID-19 have a considerably greater mortality rate as well as a higher incidence of multiple organ failure (MOF) and premature organ failure (POF) (46). Certain patients with COVID-19 infection present minor pancreatic injury (47). During COVID-19 infection, pancreatic damage or AP may manifest, especially in patients with diabetes mellitus (DM) (48). Patients with both AP and COVID-19 exhibit a higher likelihood of developing SAP/being admitted to ICU (49). Patients with COVID-19 who have AP at the time of admission have a more benign course and better overall outcomes than patients who develop AP in the hospital (50). In addition, a study by Karaali and Topal (49) on the prognosis of pancreatitis and COVID-19 revealed that patients with AP and COVID-19 have a higher rate of ICU hospitalization (7.2 vs. 0.9%) and SAP than COVID-19-negative patients (32.5 vs. 14.1%). Additionally, COVID-19 infection had a substantial and detrimental impact on mortality (49). COVID-19 therapies can cause AP both directly (through steroids and baricitinib, for example) and indirectly (by hypertriglyceridemia caused by tocilizumab and lopinavir/ritonavir, for example) (51).

Therefore, even though AP is not the most common COVID-19 symptom, it should be included as a differential diagnosis for patients with gastrointestinal symptoms, particularly abdominal pain.

## 5. AP during the COVID-19 pandemic

The COVID-19 pandemic has caused fear, which has been amplified by media showing overcrowded hospitals and helpless doctors (52). This has delayed presentation of patients to medical facilities (53) and may be associated with loss of life due to conditions such as stroke and myocardial infarction, the severity of which is decreased by emergency presentation to a hospital (54).

Early and accurate assessment of AP severity is key to prevent progression and adverse clinical outcomes by decreasing time to diagnosis and improving disease management (55).

The pandemic led to a decrease in the general hospitalization rate of patients with various conditions due to fear. A decrease in the total number of hospitalizations of patients with AP was observed compared with before the pandemic (56,57). A potential reason is that instances with a moderately severe

type of acute pancreatitis were discharged more rapidly (57), while patients with a mild form, as defined by the updated Atlanta classification (58), were no longer hospitalized. According to studies comparing hospitalizations for AP before the pandemic with hospitalizations during the pandemic, more severe forms of AP were present at the time of presentation in hospitals during the pandemic (56) and patients were more likely to develop systemic inflammatory response syndrome (40% vs. 25%) and pancreatic necrosis (14% vs. 10%) during this time (59).

## 6. COVID-19 vaccine and pancreatitis

A key advancement in public health during the past century is the development of vaccines. There are side effects to many immunizations. The onset of pancreatitis is one of these unfavorable outcomes. Numerous examples of SAP following an mRNA-based vaccine have been documented (60-65). However, Ozaka *et al* (61) and Walter *et al* (62) documented one case each of necrotizing pancreatitis. The phase II/clinical study of the COVID-19 mRNA vaccine saw one instance of pancreatitis and one case of obstructive pancreatitis as adverse effects, according to Pfizer (62,63).

According to a previous study, which involved ~38,000 people, pancreatitis is a relatively uncommon adverse event following vaccination (66). The United Kingdom revealed 275,820 reports of adverse reactions between December 9, 2020, and July 21, 2021, including 18 cases of mild AP and one case of necrotizing pancreatitis (67). Agence Nationale de Sécurité du Médicament and des Produits de Santé in France reported 57 cases of SAP out of a total of 42,523,573 doses (67). A total of 298 cases of AP and 17 cases of necrotizing pancreatitis are recorded in VigiBase, the World Health Organisation global database of individual case safety reports (68). A total of 497 gastrointestinal adverse events, or 14.1% of all observations in 2021, are reported by the Italian pharmaceutical agency Agenzia Italiana del Farmaco, however the number of AP cases is not stated (68).

In cases where AP occurs following COVID-19 vaccination with viral mRNA, direct cytopathic effects cannot explain damage to pancreatic tissue and the resulting AP; however, antigen mimicry and induced inflammation can lead to immune system activation that may be considered etiological factors of AP (69).

Although it is challenging to draw conclusions about the likelihood that the vaccine is the cause of pancreatitis, it is key to monitor underreported side effects until there are extensive data for long-term and rare side effects. Preliminary findings show that individuals who received the SARS-CoV-2 vaccine have a lower risk of severe types of AP (69) compared with patients who have not undergone vaccination.

## 7. Diagnostic and therapeutic approach

Since pancreatitis in COVID-19-positive patients occurs more frequently in severe forms, treatment must be intensive and prompt. Identification of patients with potential SAP who require a comprehensive strategy and earlier, more aggressive therapy is also essential (70,71). A worse prognosis is associated with elevated pancreatic enzyme levels in patients

with COVID-19 (71). Recent research demonstrates that although only a small percentage of critically ill patients with COVID-19 proceed to AP, the increase of pancreatic enzyme levels is significant (72). AP may be managed and monitored using C-reactive protein due to its quick reaction to changes in the intensity of the inflammatory process. Despite being associated with severity and lacking any specificity, C-reactive protein cannot be utilized to forecast how a clinical condition may develop (72).

Other markers that can be used in the prognosis of patients with acute pancreatitis are neutrophil/lymphocyte ratio (NLR), derived (d)NLR, monocyte/LR (MLR), IIC and MCV/lymphocyte ratio (MCVL). NLR shows the systemic inflammatory state having prognostic value also in patients with AP (73). Jeon and Park (74) showed that NLR may be associated with the severity of AP and multiple organ failure.

dNLR has been studied in evaluating the prognosis of patients with metastatic disease, regardless of the treatment followed (75). It has not been shown to be a prognostic factor for mortality in AP, with a specificity of <50% (56).

MLR is associated with various infectious and inflammatory diseases and is associated with the systemic inflammatory response, which reflects the immune status of the disease (76,77). MLR is associated with unfavourable outcomes in colorectal and urological cancer (78,79) and in patients with AP it proved to be a reliable marker in the prediction of complications (56).

A recent study identified two inflammatory markers, including cumulative inflammatory index, which is associated with mortality, and MCVL, which has good ability to predict surgical complications of AP; these markers have been verified both in the pre-pandemic period and during the pandemic (56).

One of the indicators used to predict the onset of SAP is serum procalcitonin, an increase in which is associated with pancreatic necrosis superinfection caused by bacteria (80). Contrast-enhanced computed tomography is the gold standard for the diagnosis of AP to assess both pancreatic and extra-pancreatic changes in patients with or without SARS-CoV-2 disease. The majority of COVID-19-positive patients with AP fulfil the updated Atlanta classification, which makes a clinical distinction between mild, moderate and SAP (14). To predict severity of AP, a number of grading systems have been created, but none is considered to be the gold standard. Early intravenous hydration is essential in the first 12-24 h after the onset of symptoms, after which its benefit decreases significantly (81,82). The maintenance of microcirculation may be associated with resolution of multiple organ failure (83,84), particularly in patients with COVID-19 and AP. Early fluid resuscitation is advised to promote tissue perfusion to treat fluid loss from third-space displacements, vomiting and increased vascular permeability (85). Çolak and Çiftci (86) showed that during the pandemic, patients treated for acute biliary pancreatitis had significantly higher lactate levels compared with pre-pandemic period, which may be related to adequate fluid replacement. Patients with AP safely receive enteral nutrition (87).

Because there is a wide variety of potential clinical courses due to involvement of different organs and tissue, it is key to

define and stratify the severity of disease in patients with AP. Laboratory tests can be used to confirm the diagnosis of AP, however the limited predictive value of assessment methods makes them clinically irrelevant (70).

The correct initial assessment of the severity of AP is key to establish additional medical treatment, which consists mainly of replacing the intravenous fluid lost as a result of its migration into the third space, increased vascular permeability and vomiting (87).

Proton pump inhibitors (PPIs) are the most effective inhibitors of stomach acid secretion and are commonly used to treat gastroesophageal reflux disease and peptic ulcers (70,88). Patients with severe AP, especially those requiring intensive care treatment or mechanical ventilation, have a predisposition to develop acute stress-associated gastric mucosal lesions (88). According to a study by Dang *et al* (88), pantoprazole decreases tissue infiltration of inflammatory cells and necrosis of acinar cells in rats with SAP. According to a study by Darnell *et al* (89) in 2004, increased acidity of the stomach (pH<3) leads to the complete inactivation of SARS-CoV, which was confirmed by Zhou *et al* (35) who found that viruses that are variants with the spike protein are completely inactivated at pH values of 1.0 and 2.0. The use of PPIs that decrease gastric acidity increases the chance of SARS-CoV-2 entering the bowel via cells that have high expression of ACE2 receptors (90), which would increase the chances of fecal-oral transmission. The occurrence of nosocomial COVID in immunocompromised patients under conditions where strict precautions were taken to prevent virus contamination by air could be explained by exogenous or cross-infection, which is caused by agents that come directly from the environment through the hands of medical personnel or contaminated objects (91).

A 2019 study by Michaelis *et al* (92) showed that omeprazole increases the antiviral activity of acyclovir against herpes simplex. Omeprazole was administered to the culture of SARS-CoV-2 cells at a therapeutic plasma concentration because it inhibits the formation of double-stranded DNA (93,94). The results of the aforementioned study led to the addition of PPIs to the COVID-19 treatment protocol because omeprazole increased therapeutic efficiency by 2 to 7 times compared with aprotinin and by 10 times that of remdesivir. PPI use increases the risk of gastrointestinal infection and favors bacterial overgrowth in the small intestine (95,96).

Antibiotics were used to treat 74% of patients with COVID-19 according to an article that assessed 19 studies comprising 2,834 patients, while only 17.6% of patients have secondary infection (97). Another meta-analysis showed that only 7% of hospitalized patients with COVID-19 have bacterial co-infection (98). The aforementioned studies show that only a few patients with COVID-19 need antibiotics for bacterial pneumonia or other co-infection. One reason for the widely used antibiotic treatment would be that for patients who are seriously ill, the diagnosis of a potential bacterial infection is uncertain, so doctors tend to use broad-spectrum antibiotics (99).

In AP, the use and effectiveness of prophylactic antibiotic therapy is a point of controversy because it is intended to prevent pancreatic infection. Initial studies have suggested that the use of prophylactic antibiotics in patients with AP is not associated with a significant decrease in morbidity or

mortality (100-102), therefore prophylactic antibiotics are no longer recommended for all patients with AP.

Antibiotic treatment in patients with AP is recommended for patients with infected AP, but its diagnosis is challenging because it cannot be distinguished from other infectious complications or the existing inflammatory state (103). With two peaks in the second to fourth week after the initiation of AP, pancreatic necrosis infection can occur at any moment and is unpredictable (104,105). Pathogenic agents that lead to the infection of necroses can reach the pancreas either by hematogenous route, through the biliary system, by ascending from the duodenum via the main pancreatic duct or by transmural colonic migration through the translocation of intestinal bacteria (106).

When pancreatic necrosis becomes infected, percutaneous catheter drainage is recommended as the first line of treatment. Diaz *et al* (107) performed a systematic review that showed that percutaneous drainage can have increased efficiency compared with patients without drainage, so that up to 71% of patients no longer require post-drainage surgery.

There is a broad consensus that surgery should be performed as late as possible (80) in cases of SAP. When percutaneous drainage does not resolve the infection, management consists of open, minimally invasive or endoscopic surgery or a combination of these. A systematic review by Gurusamy *et al* (108) showed that minimally invasive therapeutic methods used separately or in combination (result in less new-onset multiple organ failure, but nevertheless the mortality rate did not vary significantly (109,110).

Surgical intervention in AP is recommended when pancreatic necrosis becomes infected. Meta-analysis by the Eastern Association of the Surgery of Trauma comparing early with late surgery found that late surgery resulted in a clear survival benefit (111), explained by easier separation of necrotic from adjacent tissue leading to more effective necrosectomy. It is hypothesised that open surgery causes a more severe systemic inflammatory response (111).

In patients who test positive for COVID-19, AP severity bedside index cannot determine the severity of the condition (42). In addition, adding probiotics to enteral nutrition may decrease septic complications. Early enteral feeding is associated with earlier release from ventilator support, shorter ICU and hospital stay and lower cost in patients with COVID-19 requiring mechanical ventilation (112,113).

Treatment for AP in COVID-19 infection is similar to treatment for AP in general and involves intravenous fluid, analgesics, antiemetics, early resumption of nutrition and antiviral treatment for COVID-19 (112).

Patients with COVID-19 in the early stages of the pandemic, especially those with severe pneumonia and those considered to be highly contagious, did not receive endoscopic ultrasonography or therapies. Patients who had COVID-19 and AP received percutaneous and endoscopic procedures similar to those subsequently administered to patients who are negative for COVID-19, taking the necessary safety precautions (113).

Limiting surgery to patients who are already critically ill may reduce the incidence of complications and death (114,115). Patients with COVID-19-related pulmonary symptoms and injuries underwent open surgical debridement, although only a

limited percentage of them were candidates due to significant OF that made surgery impossible (67).

## 8. Conclusions

Clinical conditions may deteriorate due to COVID-19 infection. It is difficult to say if SARS-CoV-2 causes acute pancreatitis. Most cases of AP in COVID-19-positive patients are idiopathic and there is insufficient data to suggest that SARS-CoV-2 has a detrimental effect on prognosis (5). On the other hand, due to lung damage and more severe pancreatitis, AP with concurrent SARS-CoV-2 is more likely to have worse results. The serum amylase levels are not considered as a standard in the diagnosis of AP with COVID-19 due to the fact that there is a large number of patients with COVID-19 who have elevated amylase values without a pancreas disorder (5). Computed tomography is the diagnostic gold standard for these patients. A multidisciplinary team is best able to manage COVID-19-positive patients with pancreatitis due to the complexity of the condition (23). Ideally, surgical options should be scaled from the least to the most invasive. As necrotizing pancreatitis is a heterogeneous disease with noticeable differences in extent and course, surgical necrosectomy is therefore the last resort. This also implies that there is no universal approach to treatment. In conclusion, SARS-CoV-2 can directly infect pancreatic cells, but COVID-19-induced immunological activation increases the risk of pancreatitis.

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## Authors' contributions

VP, DCC, MMF, IMV, PMR, DNF, DR, RP and ICE analysed data and wrote and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

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## Competing interests

The authors declare that they have no competing interests.

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