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REVIEW

A bimodal pattern of the onset of COVID-19 related acute pancreatitis supports both the cytotoxic and immune-related pathogenesis – a systematic review

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ABSTRACT

Objectives: To review clinical and laboratory findings in patients with SARS-Cov-2 (COVID-19) related acute pancreatitis.

Methods: This systematic review was based on a database search for articles of COVID-19 related acute pancreatitis in adult patients with confirmed COVID-19 infection that included age, gender, presenting symptoms, the onset of symptoms, laboratory values, imaging findings and exclusion of common causes of pancreatitis.

Results: Altogether 35 articles comprising 37 patients were included. Acute pancreatitis was the first presentation of COVID-19 in 43% of patients, concurrent with general or respiratory symptoms in 14% of patients or delayed after general or pulmonary symptoms by an average of 10 ± 5 d (range, 1 – 19 d) in 43% of patients. Serum amylase and lipase levels were elevated in 87% and 100% of patients. In 50% and 84%, amylase and lipase levels exceeded three-fold the upper normal limit. Pancreatic necrosis was reported in 6% of patients and in 12% of patients, the pancreas appeared normal. Three patients died.

Conclusions: We conclude that the bi-modal pattern of the onset of symptoms supports both the cytotoxic and the immune-related pathogenesis of the pancreatic injury. Acute pancreatitis may be the first symptom of COVID-19 infection. Necrosis of the pancreas is rare.

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COVID-19; SARS-Cov-2; pancreatitis; lipase; computed tomography

Introduction

Pancreatic injury has been reported in a minority of patients with SARS-CoV-2 (COVID-19) infection. However, the data are sparse. In an early study from Wuhan, China, Liu et al. reported that 5 of 67 patients treated for severe COVID-19 infection had detectable changes on CT suggestive of pancreatic inflammation [1]. Apart from that, the evidence is based on scattered case reports only.

Abdominal symptoms have been reported in up to 25% of patients with COVID-19 [2,3]. They have attributed to the general status of the patient or a direct cytotoxic injury to the mucosa, which contains the target receptor (angiotensin-converting enzyme 2 [ACE2]). ACE2 is expressed in pancreatic islet cells even at greater levels than in the lungs [1]. Pancreatic involvement in COVID-19 patients has been explained by two mechanisms – the direct cytotoxic effect of the virus or a delayed injury by the immune response [4,5]. Acute pancreatic injury, cytokine storm and lipolysis have been implicated in increased mortality and morbidity across COVID-19 patients [5,6].

The aim of this systematic review was to determine the clinical, imaging and laboratory features of adult patients with COVID-19 related acute pancreatitis.

Methods

This project was approved by the Ethics Committee of the General University Hospital in Prague (ref. 2221/20 S-IV). Our methodology followed the principles recommended by the PRISMA statement for performing the systematic reviews [7].

We conducted a database search for studies dealing with acute pancreatitis and COVID-19 infection in PubMed, Web of Science, Scopus and Cohrane Library with the following terms: 'pancreatitis' AND 'COVID' and their synonyms published from January 2020 until January 2021. The search was performed across all available items written in English that were indexed in the databases.

PubMed: Query: ('pancreatitis'[All Fields]) AND ('sars cov 2'[All Fields] OR 'covid'[All Fields] OR 'covid 19'[All Fields]). Returned: 101 results.

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Supplemental data for this article can be accessed here.

Web of Science: Query: (pancreatitis COVID) OR (pancreatitis 'SARS CoV-2'). Returned: 88 results.

Scopus: Query: (pancreatitis COVID) OR (pancreatitis 'SARS CoV-2'). Returned: 147 results.

Cochrane Library: Query: (pancreatitis COVID) OR (pancreatitis 'SARS CoV-2'). Returned: 10 results.

The abstracts (or full-texts when abstract was not available) and article titles were screened for reports of COVID-19 related acute pancreatitis in adult patients with COVID-19 infection. In these articles, full-text was retrieved. In the final analysis, cases with COVID-19 infection confirmed by PCR or antigen test, that would include the following data: age, gender, presenting symptoms, the onset of symptoms, laboratory values, imaging findings and exclusion of other common causes of pancreatitis (biliary, alcoholic, binge eating and trauma) were included (Figure 1). The diagnosis of pancreatitis was based on the revised Atlanta criteria requiring $\geq$2 of (1) abdominal pain, (2) elevated serum amylase (AMS) or lipase (LPS) $>3\times$ the upper normal limit, and 3) characteristic findings on diagnostic imaging [8].

The results were expressed as nominal values for each finding or category. A meta-analysis was not attempted due to the heterogeneity of the reports.

Results

The final collection included 35 articles in a form of case reports ($n = 28$), or letters to the editor ($n = 7$) comprising 37 patients, 18 women (2 pregnant) and 19 men. Their average age was 49 ± 16 years (range, $20 - 78$ years). The reports and their findings are reported in Supplementary Material and summarized in Tables 1 and 2.

Case reports found by database search reported abdominal or epigastric pain, vomiting, fever and nausea as the most common symptoms associated with COVID-19 pancreatitis. Unspecific gastrointestinal symptoms (diarrhea, vomiting, nausea and anorexia) were present in 26 (73%) patients (Table 1).

Acute pancreatitis was the first presentation of COVID-19 in 16 (43%) patients, concurrent with general or respiratory symptoms in 5 (14%) patients or delayed after general or pulmonary symptoms by an average of 10 ± 5 d (range, $1 - 19$ d) in 16 (43%) patients.

Serum amylase and lipase levels were elevated in 26 of 30 (87%) and 31 of 31 (100%) patients, where the data were available, respectively. In 15 of 30 (50%) and 26 of 31 (84%), the amylase and lipase levels exceeded three-fold the upper normal limit. CRP levels were elevated in 20 of 20 (100%) patients and in 9 of 20 (45%) exceeded 100 mg/L. White blood cell counts were increased in 9 of 23 (39%) patients, and in 3 of 23 (13%), they exceeded 15×10^9/L (Table 2).

The pancreas was visualized in 34 of 37 (92%) patients, in 33 of 34 (97%) by CT, in one (3%) by ultrasound. The most common findings on imaging were enlarged edematous pancreas in 23 of 34 (68%) patients, stranding of peripancreatic fat in 12 (35%), peripancreatic fluid in 10 (29%), pancreatic necrosis in 2 (6%). Three (9%) reports stated a finding of acute pancreatitis. In four (12%) patients, the pancreas appeared normal. All but one patient (97%) satisfied at least two criteria for the diagnosis of acute pancreatitis set by the revised Atlanta classification.

Imaging of the lungs by chest X-ray or chest CT was reported in 32 of 37 (86%) patients and probable or typical findings of lung involvement by COVID-19 were reported in 28 (88%) of them.

The outcome was fatal in three patients, thirty-one patients recovered, and in three the outcome was not concluded.

Discussion

In this review, we summarized available reports of patients with acute pancreatitis linked to the COVID-19 infection.

The most common causes of acute pancreatitis are gallstones and alcohol intake, but about 10% of the cases are caused by infectious agents [9]. Inamdar et al. showed that in patients with COVID-19, the etiology of pancreatitis is mostly unknown (69% patients) in contrast to non-COVID-19 patients, where alcohol consumption and gallstones are the main culprits [2]. Previously, the association of pancreatitis-like symptoms in patients with COVID-19 was suggested by Spinelli and Pellino [10].

Wang et al. identified in their series of 52 patients with COVID-19 infection from the University Hospital in Wuhan, China, nine patients with pancreatic injury defined as any abnormality in amylase or lipase levels [11]. In their retrospective analysis, Barlass et al. found markedly elevated lipase levels in 14 of 83 (17%) patients who tested positive for COVID-19 and were admitted to the hospital [12]. As pointed by Pezzili et al. [13], patients with COVID-19 infection may exhibit elevation of serum levels of pancreatic enzymes but they may not satisfy the diagnostic criteria for acute pancreatitis. In their cohort of 110 COVID-19 positive patients, 24.5% of them had increased amylase levels, 16.4% had increased lipase levels, but only a single patient (0.9%) had levels above three-fold the upper limit. None of these patients developed clinical or morphological signs of acute pancreatitis [13]. The clinical significance of increased lipase levels in patients with COVID-19 has been questioned [14,15]. In the reviewed reports, either AMS or LPS were elevated in all but two patients, and 88% had evidence of pancreatitis on imaging because these are two of the three pillars of the diagnosis of acute pancreatitis according to the revised Atlanta consensus [8]. At least two of the Atlanta consensus criteria were satisfied in 97% of patients.

Liu et al. reported that 5 of 67 (7.5%) patients treated for severe COVID-19 in Wuhan, China, had detectable changes on CT suggestive of pancreatic inflammation (pancreatic enlargement, dilation of the pancreatic duct, but not pancreatic necrosis) [1]. In the presented review, pancreatic necrosis was also rare as it was reported in two (6%) patients. The mortality in the reviewed cases was 9%, which is higher than the mortality in unselected patients with COVID-19 and rather reflects that of acute pancreatitis.

The pancreatic injury in COVID-19 has been linked to the expression of ACE2 in the pancreatic islet cells. ACE2

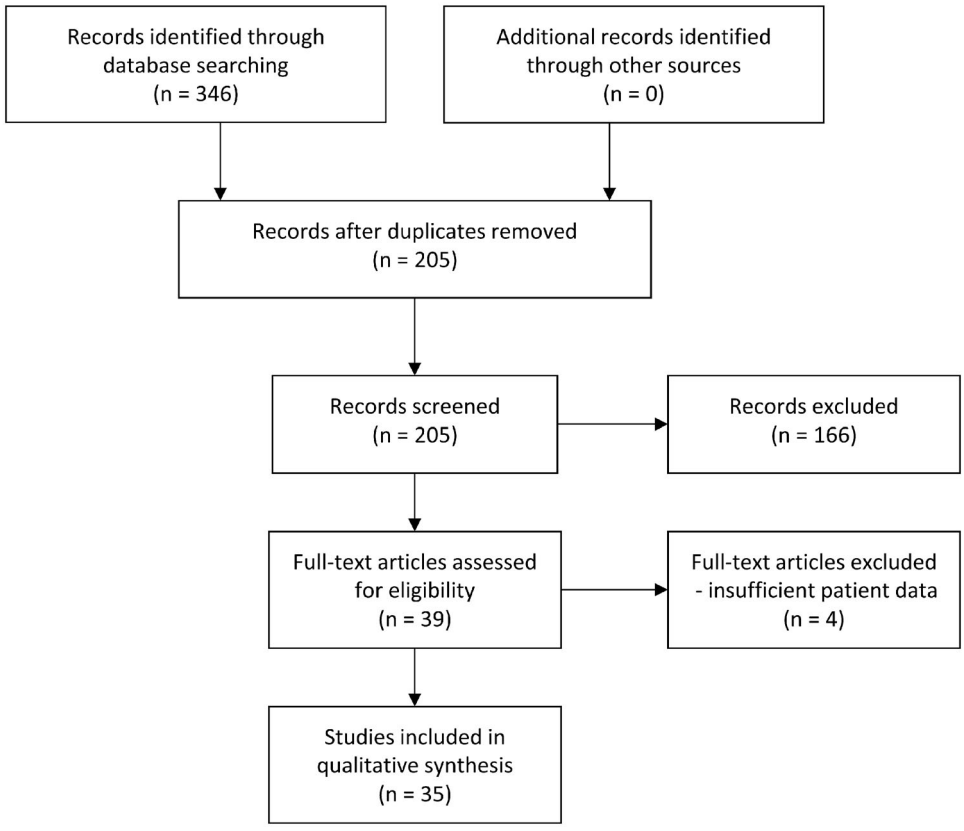

Figure 1. Database search flowchart.

Table 1. Summary of clinical symptoms in patients with COVID-19 related acute pancreatitis.

Symptom	Frequency
Pain	
Epigastric pain	26 (70%)
- Radiation to back	9 (24%)
- Belt like pain	2 (5%)
Abdominal pain	8 (22%)
Other symptoms	
Vomiting	20 (54%)
Fever	18 (49%)
Nausea	17 (46%)
Diarrhea	8 (22%)
Chills	3 (8%)
Anorexia	3 (8%)
Constipation	2 (5%)
Polydipsia	1 (3%)
No symptoms (sedation)	1 (3%)

Table 2. Summary of the levels of serum amylase, lipase, C-reactive protein and white blood cell count.

	Reported in # patients	Normal in #	Elevated in #	Markedly elevated in #
AMS	30 (81%)	4 (13%)	11 (37%)	15 (50%) [$>3 \times$ UL]
LPS	31 (84%)	0	5 (16%)	26 (84%) [$>3 \times$UL]
CRP	20 (54%)	0	11 (55%)	9 (45%) [>100 mg/L]
WBC	23 (62%)	14 (61%)	6 (26%)	3 (13%) [$>15 \times 10^9$/L]

AMS: serum amylase; LPS: serum lipase; CRP: C-reactive protein; WBC: white blood cell count; $3 \times$ UL: $3 \times$ upper normal limit; #: number.

receptor is the target receptor for COVID-19 and its expression is even higher in the pancreas than in the lungs [1]. Apart from the direct cytopathogenic effect of COVID-19, other mechanisms including systemic inflammatory response to respiratory failure or drug-related pancreatic injury may be involved [11]. Meireles et al. support the theory of secondary immune-mediated inflammatory response because the clinical symptoms of pancreatitis in their case and several other reported cases developed during resolution of the lung infection 1–2 weeks after the first respiratory or general symptoms of COVID-19 had appeared [16]. In this review, a delayed onset was found in 43% of patients. This bi-modal pattern supports both the cytotoxic and the immune-related pathogenesis of the pancreatic injury. As yet, no direct evidence of the proposed mechanism of the immune-related pancreatic injury in COVID-19 has been established. Although the direct involvement of the pancreas by COVID-19 has been reported, it is unknown, whether the virus could replicate in the pancreatic tissue.

A high association of gastrointestinal symptoms and COVID-19 in up to 79% of the patients has been reported [17]. The most-reported abdominal symptoms in the reviewed collection included abdominal (epigastric) pain, in some patients with belt-like irradiation, nausea, vomiting and diarrhea. This overlap of symptoms can be explained by the fact that the target ACE2 receptor is expressed both in the pancreas and gastrointestinal epithelial cells [18,19]. In the reviewed reports, unspecific gastrointestinal symptoms (diarrhea, vomiting, nausea, anorexia) were present in 73% of patients.

The quality and consistency of the reports was the major limitation of this review. Numerous reports did not state the normal upper values for laboratory findings. Two reports had inconsistencies in laboratory values and their interpretation. The description of imaging findings was limited to 'acute

pancreatitis' in three reports. In several reports, the timing of the onset of abdominal symptoms was concealed in the narrative. Although the reports claimed that other common causes of acute pancreatitis had been excluded (by patient's history, blood analysis and imaging), an overlap with less frequent etiologies (autoimmune, medications) could not be excluded at least in some of them. For these reasons, we did not attempt to perform a meta-analysis due to an overall small number of patients and the quality of the reports.

Conclusion

We have been able to find reports of 37 patients with COVID-19 related pancreatitis. These reports show a bi-modal pattern of the onset of gastrointestinal symptoms, which supports both the cytotoxic and the immune-related pathogenesis of the pancreatic injury. Acute pancreatitis may also be the first symptom of COVID-19 infection. The association between pancreatic injury and gastrointestinal symptoms is strong as it is in acute pancreatitis of any etiology. Necrosis of the pancreas is however rare. Future studies aimed at etiological workup, symptoms and their onset, imaging and laboratory findings in patients with COVID-19 are required to corroborate the validity of this review.

Disclosure statement

The authors declare that they have no conflict of interest regarding the publication of this work.

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