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Contents

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REVIEW

Review on acute pancreatitis attributed to COVID-19 infection

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Abstract

The coronavirus disease 2019 (COVID-19) is known to cause gastrointestinal symptoms. Recent studies have revealed COVID-19-attributed acute pancreatitis (AP). However, clinical characteristics of COVID-19-attributed AP remain unclear. We performed a narrative review to elucidate relation between COVID-19 and AP using the PubMed database. Some basic and pathological reports revealed expression of angiotensin-converting enzyme 2 and transmembrane protease serine 2, key proteins that aid in the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the pancreas. The experimental and pathological evaluation suggested that SARS-CoV-2 infects human endocrine and exocrine pancreas cells, and thus, SARS-CoV-2 may have a direct involvement in pancreatic disorders. Additionally, systemic inflammation, especially in children, may cause AP. Levels of immune mediators associated with AP, including interleukin (IL)-1β, IL-10, interferon-γ, monocyte chemotactic protein 1, and tumor necrosis factor-α are higher in the plasma of patients with COVID-19, that suggests an indirect involvement of the pancreas. In real-world settings, some clinical features of AP complicate COVID-19, such as a high complication rate of pancreatic necrosis, severe AP, and high mortality. However, clinical features of COVID-19-attributed AP remain uncertain due to insufficient research on etiologies of AP. Therefore, high-quality clinical studies and case reports that specify methods for differential diagnoses of other etiologies of AP are needed.

Key Words: COVID-19; SARS-CoV-2; Pancreatitis; Revised atlanta classification; Prognosis; Etiology

Core Tip: Several review articles have explored the relationship between coronavirus disease 2019 (COVID-19) and acute pancreatitis (AP). However, due to various etiologies associated with AP, COVID-19-attributed AP is controversially defined. Therefore, this narrative review attempted to reveal clinical features of COVID-19-attributed AP focused on surveillance of the other etiologies of AP. The clinical features of COVID-19-attributed AP remain uncertain due to insufficient data on etiologies of AP. Therefore, prospective cohort studies focused on patients with COVID-19 with idiopathic AP are required, especially to clearly exclude other etiologies of AP.

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INTRODUCTION

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. COVID-19 causes respiratory symptoms, such as cough, fever, sputum production, and shortness of breath, and also leads to gastrointestinal symptoms, such as nausea, vomiting, and diarrhea [1,2]. Some studies revealed that SARS-CoV-2 RNA can be detected in the gastrointestinal tract[3,4]. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) protein that serves as an entry point for the virus into epithelial cells[5]. SARS-CoV-2 also invades the gastrointestinal tract *via* ACE2, allowing development of gastrointestinal symptoms[2,6-9]. Recent studies suggest that SARS-CoV-2 infection might induce pancreatic injury or acute pancreatitis (AP)[10,11]. Schepis *et al*[12] identified SARS-CoV-2 RNA in a pancreatic pseudocyst sample collected from a patient with COVID-19[12]. Moreover, ACE2 expressed in the pancreas is associated with pancreatic injury[13]. In experimental system, SARS-CoV-2 infects human endocrine and exocrine cells of the pancreas, *ex vivo* and *in vivo*[14]. However, clinical features of COVID-19-attributed AP remain uncertain. Some systematic reviews have reported COVID-19-attributed pancreatic injury[15,16], but it remains uncertain whether the pancreatic injury is truly caused by SARS-CoV-2 due to insufficient search for the etiology of AP. Gallstones and alcoholism are two common etiological factors of AP[17-19]. Certain medications (valproic acid, azathioprine, and sulfonamides), metabolic disturbances (hypercalcemia and hypertriglyceridemia), and infections are also rare etiologies[19,20]. Trauma, iatrogenic considerations [*e.g.*, endoscopic retrograde cholangiopancreatography (ERCP)], anatomy (*e.g.*, pancreatic tumor or pancreatic divisum), ischemia/reperfusion, and genetic mutation are also reported as etiologies of AP[19,21-23]. Many studies have reported that bacterial, mycobacterial, helminthic, protozoan, and fungal infections are etiologies of AP[24,25]. Furthermore, hepatotropic virus, Coxsackie virus, Echovirus, Cytomegalovirus, human immunodeficiency virus, Herpes simplex virus, mumps virus, measles virus, varicella-zoster virus, and other viruses may cause infectious AP[24-26]. Therefore, the COVID-19-attributed AP should be diagnosed by sufficient exclusion of other etiologies of AP. Additionally, the diagnostic criteria for COVID-19 is reverse transcription-polymerase chain reaction (RT-PCR) or serological test for SARS-CoV-2, and also clinical examinations, such as chest computed tomography (CT) and clinical history. Moreover, the diagnostic criteria for AP and severity of COVID-19 and AP are not unified across reports. Thus, it is required to sufficiently evaluate etiologies of AP, and clearly define diagnostic and severity criteria of COVID-19 and AP for reviewing COVID-19-attributed AP. A sufficient evaluation of etiologies of AP should be performed, especially in case studies.

This study aimed to perform a review of literature to reveal recent findings on the association between AP and SARS-CoV-2. The review also focusses on the real-world data of COVID-19-attributed AP, with surveillance for other etiologies of AP, and reveals some clinical features of COVID-19-attributed AP.

MECHANISMS OF AP WITH COVID-19

Direct association between the pancreas and SARS-CoV-2

Coronaviruses constantly circulate in human populations and usually cause mild respiratory symptoms. The gastrointestinal symptoms, although not as common as respiratory symptoms, have been observed in some patients with COVID-19[2]. The SARS-CoV-2 depends on ACE2, a protein that binds to viral spike (S) protein, to enter epithelial cells[5]. SARS-CoV-2 also invades the gastrointestinal tract *via* ACE2

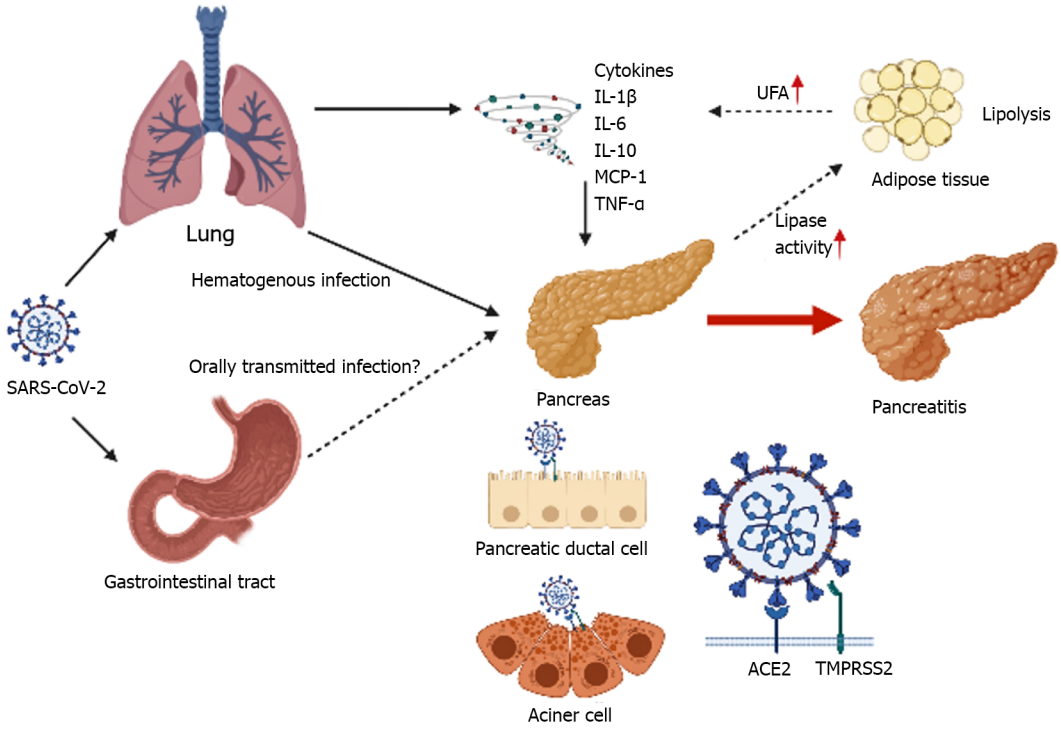

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Figure 1 Direct and indirect pathways of pancreatic injury caused by severe acute respiratory syndrome coronavirus-2. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disseminates through the bloodstream mainly to the pancreas. SARS-CoV-2 may be transported to the pancreas *via* the gastrointestinal tract. The pancreas expresses angiotensin converting enzyme-2 (ACE2) and the transmembrane protease serine 2 (TMPRSS2). SARS-CoV-2 binds to ACE2 after the viral spike (S) protein is primed by TMPRSS2 for cell entry. Therefore, SARS-CoV-2 may potentially cause direct pancreatic injury, including acute pancreatitis. However, indirect pancreatic injury may also be caused by systemic inflammatory responses from respiratory failure induced by SARS-CoV-2 infection. Levels of proinflammatory immune mediators associated with pancreatitis, including interleukin (IL)-1β, IL-6, IL-10, interferon-γ, monocyte chemotactic protein-1, and tumor necrosis factor-α are higher in the plasma of patients with coronavirus disease 2019. These mediators may indirectly cause pancreatic injury. An increase in lipase activity triggers lipolysis in the adipose tissues, and enhances levels of serum unsaturated fatty acids (UFA). UFA may cause an increase in levels of proinflammatory immune mediators that lead to systemic inflammation. SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; ACE2: Angiotensin converting enzyme-2; TMPRSS2: Transmembrane protease serine 2; IL: Interleukin, IFN-γ: Interferon-γ; MCP-1: Monocyte chemotactic protein-1; TNF-α: Tumor necrosis factor-α; UFA: Unsaturated fatty acids.

and leads to development of gastrointestinal symptoms[2,6-9]. The pancreas also expresses ACE2, with mRNA of ACE2 being expressed in the exocrine glands and islets (Figure 1)[13,27]. The transmembrane protease serine 2 (TMPRSS2), co-expressed with ACE2, is known to be required for virus entry[5,28]. TMPRSS2 is associated with proteolytic cleavage of the viral S protein, and mediates membrane insertion of S protein and viral membrane fusion. TMPRSS2 is also expressed in the pancreas, including the pancreatic ductal epithelial cells, acinar cells, and islet cells[29,30]. According to single cell analysis of human pluripotent stem cells, ACE2 and TMPRSS2 are co-expressed in the acinar cells, ductal cells, alpha cells, and beta cells[31]. Furthermore, ACE2 protein is expressed in the islet and exocrine tissue microvasculature and in a subset of pancreatic ducts, whereas TMPRSS2 is restricted to ductal cells[30]. In tissue sections derived from the pancreas of five healthy humans, the expression of ACE2 was detected in endothelial cells, a subpopulation of ductal cells, and endocrine cells, while TMPRSS2 was detected in beta cells. However, both ACE2 and TMPRSS2 were poorly expressed in acinar cells[14]. Pathological evaluation of patients deceased due to COVID-19 identified SARS-CoV-2 positivity in some ductal cells, a few acinar cells, and endocrine cells. Therefore, SARS-CoV-2 was confirmed to infect human endocrine and exocrine cells of the pancreas, *in vivo*[14]. Moreover, infection with SARS-CoV-2 increases expression of C-X-C motif chemokine ligand 12 (CXCL12), nuclear factor kappa β subunit 1 (NFKβ1), and signal transducer and activator of transcription 3 (STAT3) that are known to be associated with pancreatitis-related inflammation[32]. Therefore, SARS-CoV-2 may directly injure the pancreas. SARS-CoV-2 is considered to primarily disseminate *via* the bloodstream, but there are no data on how SARS-CoV-2 is transported to the pancreas[15]. Some patients with COVID-19 develop AP without any respiratory symptoms at onset[33]. However, it is uncertain whether SARS-CoV-2 is transported to the pancreas *via* the gastrointestinal tract, where SARS-CoV-2 is detected in patients with COVID-19[3].

Pancreatic injury caused by SARS-CoV-2-induced cytokine storm

Recent studies reported that the rate of pancreatic enzyme elevation ranged between 12.1% and 17.3% in patients with COVID-19[10,34,35]. Wang *et al*[10] reported the first case series of COVID-19-attributed

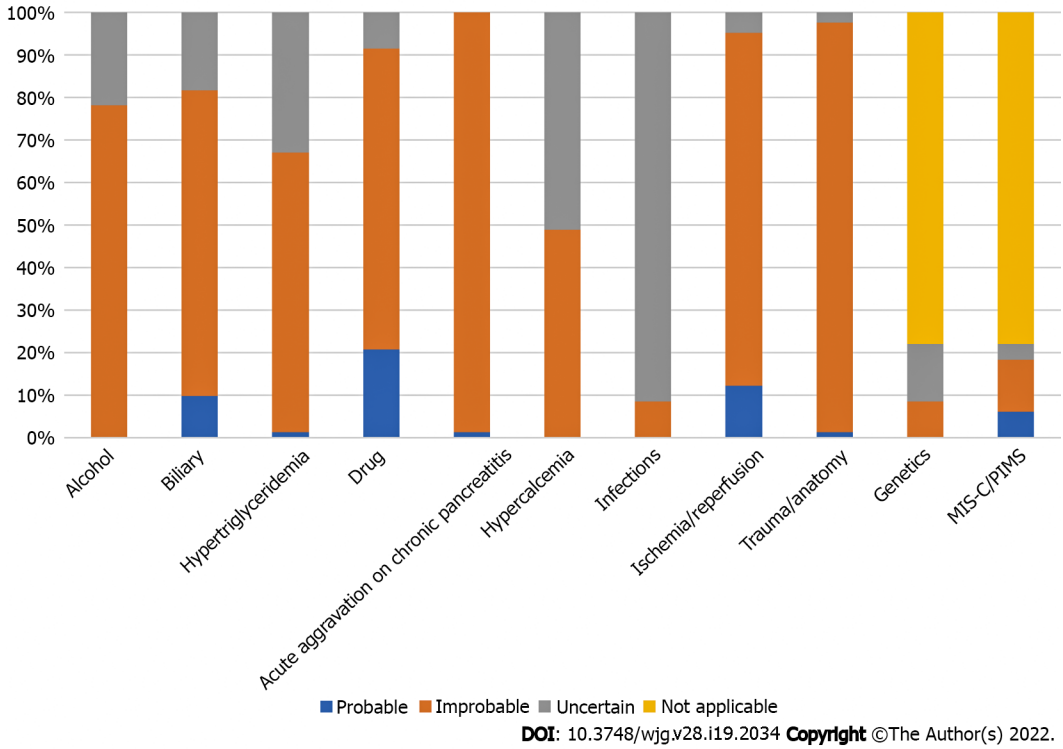

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Figure 2 The probability of other etiologies of acute pancreatitis in cases with concurrent coronavirus disease 2019 and acute pancreatitis. The potential of other etiologies, including alcoholism, biliary, hypertriglyceridemia, hypercalcemia, drug-induced, acute aggravation on chronic pancreatitis, ischemia/reperfusion, and trauma/anatomy. In children, the potential of genetic and multisystemic inflammatory syndrome in children/pediatric inflammatory multisystem syndrome-induced acute pancreatitis (AP) are also evaluated. Moreover, these causes are regarded as inapplicable etiologies of AP in adults. The probability of AP is disregarded in cases with insufficient information on the etiologies of AP. Some etiologies of AP, such as alcohol, acute aggravation on chronic pancreatitis, and trauma/anatomy are well verified. Furthermore, the etiological workup for infections and hypercalcemia is insufficient. Moreover, some cases of AP may have been caused by drug and biliary disease as it may be difficult to exclude them from the etiology of AP. MIS-C: Multisystemic inflammatory syndrome in children; PIMS: Pediatrics inflammatory multisystem syndrome; AP: Acute pancreatitis.

pancreatic injury and suggested two pathophysiological theories of how pancreatic injury was caused by SARS-CoV-2[10]. First, viral infection causes direct pancreatic injury, as described above. Second, an indirect pancreatic injury is caused by systemic inflammatory responses to respiratory failure or by harmful systemic immune response induced by SARS-CoV-2 infection (Figure 1). Severe COVID-19, including acute respiratory distress syndrome (ARDS) and multiorgan failure is also known to be associated with cytokine storms in the host[36,37]. Levels of proinflammatory immune mediators associated with pancreatitis, including interleukin (IL)-1β, IL-6, IL-10, interferon-γ (IFN-γ), monocyte chemotactic protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) are higher in the plasma of patients with COVID-19 than those in healthy controls. Furthermore, in infected patients, levels of MCP-1 and TNF-α are significantly higher requiring admission to intensive care units (ICUs) than those in patients not being treated in ICUs[2,38,39]. Another study suggested that levels of IL-6, IL-10, and TNF-α were increased in patients with severe COVID-19 than in those with non-severe COVID-19[40]. Several points remain unclear in the relationship between proinflammatory immune mediators regulated by the viral effect and AP, but serum amylase and lipase elevation in patients with COVID-19 are associated with severity of COVID-19[41-44]. Additionally, AP is also more complicated in cases with severe COVID-19 than in patients with non-severe COVID-19[45]. These facts may support that cytokine storm caused by SARS-CoV-2 induces AP. In contrast, recent research suggests that the release of pancreatic lipase is associated with an increase in levels of unsaturated fatty acids[46]. It is hypothesized that the intestinal release of pancreatic lipase increases lipolysis and plasma levels of unsaturated fatty acids that may damage mitochondria and cause an increase in proinflammatory immune mediators[47]. This increase in cytokines can accelerate disease pathogenesis and lead to severe COVID-19[41,48]. Additional research and analyses are needed to validate this hypothesis, but it is uncertain whether severe COVID-19 causes AP or complicated AP is associated with increased severity of COVID-19 or both. Moreover, severe COVID-19 may complicate AP with other etiologies, including ischemia, hypercalcemia, and drugs[48]. Corticosteroid is known to induce pancreatitis; but, drug-induced AP is observed in < 5% of total AP cases, and corticosteroid accounts for only 2.8% of the drug-induced AP cases[19,49]. Tocilizumab, an antibody for IL-6 indicated for COVID-19, is also reported as an etiology for AP[50,51].

Further, multisystemic inflammatory syndrome in children (MIS-C)/pediatric inflammatory multisystem syndrome (PIMS), novel multisystem inflammatory conditions with some features similar to those of Kawasaki disease, and toxic shock syndrome leading to multiorgan failure and shock cause gastrointestinal symptoms in children[52-54]. Recent case studies also revealed that MIS-C/PIMS may complicate AP[55-58]. An international survey on children with co-occurrence of COVID-19 and AP showed that 2 of 22 patients had MIS-C/PIMS. The mechanisms of MIS-C/PIMS are unclear, but SARS-CoV-2 may cause AP *via* inflammatory immune mediators.

REAL-WORLD DATA ON COVID-19 AND AP

Cohort and case-control studies on COVID-19 and AP

In a prospective, cohort study in the Netherlands, Bulthuis *et al*[59] confirmed COVID-19 in 433 patients with RT-PCR and/or chest CT scores[59]. Eight of the 433 patients met the Revised Atlanta Classification of AP and all were teetotalers. Three of eight patients had other etiologies (two biliary and one post-ERCP); thus, five (1.2%) were suspected with COVID-19-attributed AP. The median age of the five cases was 60 (range, 47–71) years, and 80% were men. Necrotic changes were not observed in the pancreas of the five patients. All five had organ failures, and three (60%) succumbed to non-pancreatitis-related complications of COVID-19 although their AP was not severe. Vatansev *et al*[60] reported a retrospective cohort study comprising 150 patients, of which 29 had AP, and COVID-19 was confirmed with RT-PCR[60]. The mean age of 29 patients was 64.07 years, and 18 were men. In this study, AP was defined as abdominal pain, increased serum amylase and lipase levels (values not disclosed), and contrast-enhanced abdominal CT findings. Patients with some complications and history of habits, including gallstones, hypercalcemia, hypertriglyceridemia, alcohol consumption, and chronic pancreatitis were excluded from the study. All 29 patients had respiratory failures when diagnosed with AP. According to the Revised Atlanta Classification, the severity of AP was mild and moderate in 19 and 10 cases, respectively. The mortality was 8 of 29 patients (28%) died due to respiratory failure and multiple organ failure. These findings suggest a high mortality rate in patients with COVID-19-attributed AP. However, despite a strict investigation of etiologies of AP in the latter study, the number of patients suspected with COVID-19-attributed AP was higher, although a simple comparison was not possible due to differences in COVID-19 diagnostic criteria. Nevertheless, these studies failed to exclude other etiologies of AP, such as drugs, infections except SARS-CoV-2, and ischemia/reperfusion.

Akarsu *et al*[45] investigated the impact of AP on prognosis of COVID-19 in a prospective study[45]. They included 316 patients with COVID-19, of which 40 had complicated AP with various etiologies. AP was defined according to the Revised Atlanta Classification. The study showed a positive correlation between the severity of pneumonia and AP, and indicated that the frequency of AP increased with severity of pneumonia. Moreover, the mortality rate in patients with COVID-19-attributed AP was higher than that in patients with COVID-19 without AP (32.5% *vs* 7.97%, $P < 0.0001$). These studies showed that the incidence of COVID-19-attributed AP was rare, whereas comorbid COVID-19 was severe and had poor prognosis regardless of the severity of AP. This tendency was identified in suspected COVID-19-attributed AP and also AP with other etiologies. Furthermore, as described above, it is possible that severe conditions that needed treatment at ICU, induced AP in patients with COVID-19. Interestingly, Kumar *et al*[33] focused on the difference in the onset of AP in patients with COVID-19 in a retrospective study[33]. Lipase levels were measured and COVID-19 was confirmed with RT-PCR in 985 patients; of these, 17 cases were diagnosed with AP according to the Revised Atlanta Classification. Eight of these 17 presented with typical symptoms of AP on admission. The others developed AP after the onset of COVID-19 pneumonia and treatment with mechanical ventilation for ARDS. The number of patients were less, but the mortality rate in patients who were primarily admitted for AP was higher than that in patients who developed AP later (12.5% *vs* 33.3%). Several different clinical backgrounds should be considered as the reasons, etiologies of AP also seemed to be one of the causes, and it was not clear in the study. Ischemia/reperfusion and drugs were considered as etiologies of AP in patients who developed AP later, as they were treated with mechanical ventilation for ARDS.

There are several studies on AP and SARS-CoV-2 during the COVID-19 pandemic, and some of them focused on differences in the clinical course of AP, with or without comorbid COVID-19. Pandanaboyana *et al*[61] conducted a prospective, international, multicenter, large cohort study on patients with AP and coexistent SARS-CoV-2 infection[61]. The study, called the COVID PAN collaborative study, comprised 1777 patients with AP with various etiologies, of which 149 were SARS-CoV-2 positive. The study had some limitations, such as the diagnostic criteria of AP was uncertain, although the severity of AP was based on the Revised Atlanta Classification. The most important limitation was that the criteria for diagnosis of COVID-19 was RT-PCR for SARS-CoV-2 and also chest CT images and/or clinical course. The authors performed subgroup analysis to compare outcomes between patients negative for SARS-CoV-2 and those positive for SARS-CoV-2 confirmed by RT-PCR. After exclusion of patients from the subgroup analysis due to missing values, 82 of 909 patients with AP were positive for SARS-CoV-2. The 30-d mortality, rate of persistent organ failure, and acute pancreatic fluid collection were higher, and the length of hospital stay was longer in patients positive for SARS-CoV-2 than in those negative for

Table 1 Demographic characteristic of cases with suspected coronavirus disease 2019-attributed acute pancreatitis

Patient characteristics	Value
Age, median (range, yr)	42.0 (6-87)
Gender, male/female/NA	37/44/1
Comorbidities	
Hypertension	22
Diabetes	15
Dyslipidemia	4
Heart disease	3
Cerebrovascular	0
Respiratory disease	4
Renal dysfunction	5
Obesity	16
Pregnancy	2
Malignancy	2
History of abdominal surgery	13
Others	10
Alcohol consumption, none/low/heavy/NA	53/9/0/20
History of smoking, never/experience/current/NA	32/2/0/48
Severity of COVID-19	
Non-severe/severe/critical/NA	35/23/20/4
Symptoms	
Fever	49
Breath shortness	16
Cough	28
Dyspnea	18
Sore throat	18
Fatigue	9
Headache	7
Myalgia	10
Anorexia	13
Diarrhea	16
Abdominal pain	75
Nausea	39
Vomiting	48
Others	23
Blood test	
WBC, median (range, $\times 10^3/mm^3$)	13.10 (3.40-230.00)
PLT, median (range, $\times 10^3/mm^3$)	235.5 (52.0-502.0)
D-Dimer, median (range, μg/mL)	4.9 (0.3-17.7)
Amylase, median (range, U/L)	635 (47-4530)
Lipase, median (range, U/L)	895.5 (35.6-11920.0)
LDH, median (range, U/L)	366.0 (170-3553)

CRP, median (range, mg/dL)	8.5 (0.3-59.7)
Imaging findings (*n* = 75)	
Pancreatic enlargement	42
Peripancreatic fluid collection	33
Peripancreatic inflammatory change	48
Pancreatic ischemic change	12
No change of pancreas	6
Not visualized	2
Severity of acute pancreatitis	
Mild/moderate/severe/NA	28/20/28/6
Therapy for COVID-19	
Lopinavir/ritonavir	4
Favipiravir	4
Umifenovir	2
Remdesivir	8
Hydroxychloroquine	2
Tocilizumab	2
Corticosteroid (*n* = 53)	21
Oxygen therapy (*n* = 69)	42
Mechanical ventilation	19
Therapy for acute pancreatitis	
Conservative therapy/surgical drainage/NA	72/4/6
Period of hospitalization, median (range, day)	7.5 (2-76)
Prognosis	
Alive/death/NA	69/10/3

RT-PCR: Reverse transcription polymerase chain reaction; IgM: Immunoglobulin M; IgG: Immunoglobulin G; WBC: White blood cell; PLT: Platelet; LDH: Lactate dehydrogenase; CRP: C-reactive protein; NA: Not available; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; COVID-19: Coronavirus disease 2019.

SARS-CoV-2. Three retrospective cohort studies also reported results similar to those of the COVID PAN collaborative study[62-64]. Thus, concurrent AP and SARS-CoV-2 infection may lead to worse clinical outcomes, such as prolonged hospital stay, requirement of mechanical ventilation, high incidence of multiple organ failure, and high mortality than that with AP-alone. In contrast, two of three studies also revealed that the incidence of idiopathic AP in patients positive for SARS-CoV-2 was higher than that in patients negative for SARS-CoV-2[62,63]. Interestingly, the COVID PAN collaborative study also revealed that[65] SARS-CoV-2 infection may cause AP similar to other infections. Miró *et al*[66] conducted a retrospective case-control study, called the Unusual Manifestations of COVID-19 (UMC-19) study, comprising emergency units in Spain[66]. The diagnostic criteria for AP were according to the Revised Atlanta Classification. The diagnosis of COVID-19 was based on RT-PCR or antigen detection test, and also on chest image findings and clinical conditions. In 62 emergency departments, of the 1463693 patients tested for COVID-19, 74814 cases tested positive, and 54 of them (0.072%) developed AP. Furthermore, the frequency of non-COVID-19 patients with AP was 0.161% (2231/13888879). To compare outcomes between AP and COVID-19 groups, patients were randomly distributed into two groups-162 patients with AP without COVID-19 and 162 patients without AP with COVID-19. Patients with AP with COVID-19 showed severe clinical courses with high mortality than patients without AP with COVID-19. Moreover, there were no differences in the etiologies of AP with or without concurrent SARS-CoV-2 infections. Additionally, the incidence of AP in patients with COVID-19 was lower than that in patients with AP without COVID-19, consistent with results discussed above (0.072% *vs* 0.161%). In contrast, there were no differences between patients with COVID-19 with AP and those with COVID-19 without AP, except for the length of hospitalization. These results suggest that COVID-19 affects the prognosis of patients with concurrent AP and COVID-19 than those with AP-alone. A recent meta-

Table 2 Baseline characteristics of cases with coronavirus disease 2019 and acute pancreatitis coexistent

Case No.	Ref.	Age	Gender	Diagnostic evidence for SARS-CoV-2	Severity of COVID-19	Abdominal pain	Amylase/lipase (IU/L)	Abdominal image findings	Modality of image	Severity of acute pancreatitis	Treatment for pancreatitis	Prognosis
1	Anand *et al*[70]	59	Female	RT-PCR	Non-severe	Presence	NA/NA	Diffuse pancreatic enlargement	CT	Mild	Conservative	Alive
2	Hadi *et al*[71]	47	Female	RT-PCR	Critical	Absence	1500/NA	Diffuse pancreatic enlargement	AUS	Severe	NA	NA
3	Hadi *et al*[71]	68	Female	RT-PCR	Critical	Presence	934/NA	NA	NA	Severe	NA	NA
4	Aloysius *et al*[72]	36	Female	RT-PCR	Critical	Presence	325/627	No change	CT	Severe	Conservative	Alive
5	Miao *et al*[73]	26	Female	RT-PCR	Non-severe	Presence	NA/430	Diffuse pancreatic enlargement	CT	NA	NA	Alive
6	Szatmary *et al*[74]	29	Male	RT-PCR	Non-severe	Presence	77/NA	Diffuse pancreatic enlargement, peripancreatic inflammatory change, fluid collection	CT	Moderate	Conservative	Alive
7	Szatmary *et al*[74]	47	Male	RT-PCR	Non-severe	Presence	211/NA	Diffuse pancreatic enlargement, peripancreatic inflammatory change, fluid collection	CT	Moderate	Conservative	Alive
8	Rabice *et al*[75]	36	Female	RT-PCR	Severe	Presence	88/875	Not visualized	AUS	Mild	Conservative	Alive
9	Alloway *et al*[76]	7	Female	RT-PCR	Non-severe	Presence	NA/1672	Diffuse pancreatic enlargement	AUS and CT	Mild	Conservative	Alive
10	Karimzadeh *et al* [77]	65	Female	RT-PCR	Severe	Presence	285/294	No change	CT	Mild	Conservative	Alive
11	Gonzalo-Voltas *et al*[78]	76	Male	RT-PCR	Non-severe	Presence	3568/NA	Diffuse pancreatic enlargement	CT	Moderate	Conservative	Alive
12	Bokhari *et al*[79]	32	Male	RT-PCR	Non-severe	Presence	672/721	Diffuse pancreatic enlargement, peripancreatic inflammatory change, fluid collection	CT	Mild	Conservative	Alive
13	Mazrouei *et al*[80]	24	Male	RT-PCR	Non-severe	Presence	391/578	Enlargement of pancreatic tail, peripancreatic fluid collection	CT	Mild	Conservative	Alive
14	Ahmed *et al*[81]	47	Male	RT-PCR	Severe	Presence	349/NA	Peripancreatic inflammatory change	CT	Severe	NA	Alive
15	Brikman *et al*[82]	61	Male	RT-PCR	Severe	Presence	142/203	Peripancreatic inflammatory change	CT	Mild	Conservative	Alive
16	Kataria *et al*[83]	49	Female	RT-PCR	Severe	Presence	501/1541	Diffuse pancreatic enlargement, peripancreatic fluid collection	CT	Mild	Conservative	Alive
17	Cerda-Contreras *et al*[84]	72	Female	RT-PCR	Severe	Absence	1789/1247	Diffuse pancreatic enlargement, peripancreatic inflammatory change, fluid collection	CT	Severe	Conservative	Dead

18	Cheung *et al*[85]	38	Male	RT-PCR	Non-severe	Presence	NA/338.7	Acute pancreatitis	CT	NA	Conservative	Alive
19	Kumaran *et al*[86]	67	Female	RT-PCR	Severe	Presence	1483/NA	Peripancreatic inflammatory change and fluid collection, non-enhancement of most of the head and proximal body	CT	Severe	Conservative	Alive
20	Purayil *et al*[87]	58	Male	RT-PCR	Non-severe	Presence	249/NA	Not visualized	AUS	Mild	Conservative	Alive
21	Dietrich *et al*[88]	72	Male	RT-PCR	Critical	Presence	NA/185	Normal pancreas	CT	Mild	NA	Alive
22	Patnaik *et al*[89]	29	Male	RT-PCR	Non-severe	Presence	2861/1650	Diffuse pancreatic enlargement, peripancreatic fluid collection	CT	Mild	Conservative	Alive
23	Wang *et al*[90]	42	Male	RT-PCR	Critical	Presence	132/382	Pancreatic enlargement, peripancreatic fluid collection	CT	Moderate	Conservative	Dead
24	Wang *et al*[90]	35	Male	RT-PCR	Non-severe	Presence	NA/1042	Pancreatic enlargement, peripancreatic fluid collection	CT	Moderate	Conservative	Alive
25	Alves *et al*[91]	56	Female	RT-PCR	Critical	Presence	544/2993	Dffuse pancreatic enlargement, peripancreatic inflammatory change	CT and MRI	Severe	Conservative	Alive
26	Kurihara *et al*[92]	55	Male	RT-PCR	Critical	Absence	252/263	Pancreatic enlargement, peripancreatic inflammatory change	CT	Severe	Conservative	Alive
27	Lakshmanan and Malik[93]	68	Male	RT-PCR	Non-severe	Absence	1030/2035	Peripancreatic inflammatory change	CT	Mild	Conservative	Alive
28	Samies *et al*[94]	15	Male	RT-PCR	Non-severe	Presence	NA/233	Peripancreatic inflammatory change	CT	Mild	Conservative	Alive
29	Samies *et al*[94]	11	Male	RT-PCR	Non-severe	Presence	215/953	No change	CT	Mild	Conservative	Alive
30	Samies *et al*[94]	16	Female	RT-PCR	Non-severe	Presence	NA/1909	Pancreatic enlargement	CT	Mild	Conservative	Alive
31	Fernandes *et al*[95]	36	Female	RT-PCR	NA	Presence	710/640	Pancreatic enlargement, peripancreatic fluid collection	CT	Moderate	Conservative	Alive
32	Stevens *et al*[55]	10	Female	Serological IgG	Severe	Presence	NA/1371	Peripancreatic inflammatory change	CT	Severe	Conservative	Alive
33	Shinohara *et al*[96]	58	Male	RT-PCR	Critical	Presence	795/NA	Diffuse pancreatic enlargement peripancreatic inflammatory change	CT	Moderate	Conservative	Alive
34	Meyers *et al*[97]	67	Male	RT-PCR	NA	Presence	NA/5295	Interstitial edematous pancreatitis peripancreatic inflammatory change	CT	Moderate	NA	NA
35	Ghosh *et al*[98]	63	Male	RT-PCR	Severe	Absence	58/412	Focal pancreatic enlargement, peripancreatic fluid collection	CT	NA	Conservative	Alive
36	Tollard *et al*[99]	32	Female	RT-PCR	Critical	Presence	NA/321	Diffuse pancreatic enlargement peripancreatic inflammatory change	CT	Severe	Conservative	Dead
37	Kandasamy *et al*[100]	45	Female	RT-PCR	Severe	Presence	364/293	Diffuse pancreatic enlargement, peripancreatic inflammatory change and fluid collection	CT	Moderate	Conservative	Alive

38	Hassani *et al*[101]	78	Female	RT-PCR	Critical	Presence	1200/1450	Pancreatic enlargement necrotizing pancreatitis	AUS and CT	Severe	Conservative	Dead
39	Suchman *et al*[56]	10	Female	RT-PCR	Non-severe	Presence	NA/365.7	NA	NA	Moderate	Conservative	Alive
40	Suchman *et al*[56]	16	Male	RT-PCR	Critical	Presence	NA/233.3	NA	NA	Severe	Conservative	Alive
41	Narang *et al*[102]	20	Female	RT-PCR	Severe	Presence	1168/916	Acute pancreatitis	MRI	Severe	Conservative	Alive
42	Acherjya *et al* [103]	57	Female	RT-PCR	Severe	Presence	80/8352	Diffuse pancreatic enlargement, peripancreatic inflammatory change	CT	Moderate	Conservative	Alive
43	Alwaeli *et al*[104]	30	Male	RT-PCR	Critical	Presence	151/1022	Diffuse pancreatic enlargement, peripancreatic inflammatory change	CT	Severe	Conservative	Alive
44	Simou *et al*[105]	67	NA	RT-PCR	Severe	Absence	NA/576	Diffuse pancreatic enlargement, peripancreatic inflammatory change	CT	Severe	Conservative	Dead
45	Jespersen Nizamic *et al*[106]	49	Female	RT-PCR	Non-severe	Presence	NA/2864	Peripancreatic inflammatory change, fluid collection	CT	Moderate	Conservative	Alive
46	Abraham *et al* [107]	61	Female	RT-PCR	Non-severe	Presence	NA/1018	NA	NA	Mild	Conservative	Alive
47	Abhinay *et al*[108]	13	Female	RT-PCR	NA	Presence	217/365	Peripancreatic inflammatory change, fluid collection	CT	Moderate	Conservative	Alive
48	Bouali *et al*[109]	60	Female	RT-PCR	Critical	Presence	NA/627	Peripancreatic fluid collection	CT	Severe	Drainage of abdominal cavity, total gasterectomy	Dead
49	Alharmi *et al*[110]	52	Female	RT-PCR	Non-severe	Presence	47/NA	Atrophic pancreas, peripancreatic inflammatory change, peripancreatic fluid collection	CT	Moderate	Conservative	Alive
50	Abbas *et al*[57]	13	Female	RT-PCR	Critical	Presence	217.8/NA	Fluid collection	CT	Severe	Conservative	Alive
51	Bineshfar *et al* [111]	14	Male	RT-PCR	Non-severe	Presence	1914/NA	Diffuse pancreatic enlargement, peripancreatic inflammatory change	CT	Mild	Conservative	Alive
52	Paz *et al*[112]	14	Male	RT-PCR	Non-severe	Presence	196/247	Peripancreatic inflammatory change, fluid collection	MRI	Mild	Conservative	Alive
53	Wifi *et al*[113]	72	Female	RT-PCR	Non-severe	Presence	1667/710	No change	CT	Mild	Conservative	Alive
54	Sandhu *et al*[114]	25	Female	RT-PCR	Critical	Presence	350/35.6	Diffuse pancreatic enlargement	CT	Severe	Conservative	Dead
55	Mohammadi Arbati *et al*[115]	28	Male	RT-PCR	Critical	Presence	1273/758	Peripancreatic inflammatory change, fluid collection, acute necrotic pancreatitis	CT	Severe	Conservative	Alive
56	Amé *et al*[116]	42	Female	RT-PCR	NA	Presence	2263/2799	Pancreatic enlargement, peripancreatic inflammatory change, fluid collection	CT	NA	Conservative	Alive
57	Gupta *et al*[117]	25	Female	RT-PCR	Severe	Presence	1814/11920	Diffuse pancreatic enlargement,	CT	Severe	Conservative	Alive

								peripancreatic inflammatory change, fluid collection				
58	Muhammad Abrar Jeelani *et al* [118]	24	Male	RT-PCR	Non-severe	Presence	NA/4174	Peripancreatic inflammatory change, fluid collection	CT	Moderate	Conservative	Alive
59	Maalouf *et al*[119]	62	Male	RT-PCR	Non-severe	Presence	NA/4361	Peripancreatic inflammatory change, necrotic collection	MRI	Moderate	Conservative	Alive
60	Sanchez *et al*[120]	16	Male	RT-PCR	Severe	Presence	NA/961	Peripancreatic inflammatory change, fluid collection	CT	Moderate	Conservative	Alive
61	Ehsan *et al*[121]	13	Female	RT-PCR	Severe	Presence	598/2331	Peripancreatic inflammatory change, fluid collection	CT	Moderate	Conservative	Alive
62	Hanif *et al*[122]	30	Female	RT-PCR	Severe	Presence	820/626	Diffuse pancreatic enlargement, peripancreatic inflammatory change	CT	Severe	Conservative	Alive
63	Chandra *et al* [123]	53	Male	RT-PCR	Critical	Presence	NA/1200	Peripancreatic inflammatory change	CT	Severe	Conservative	Alive
64	Alfishawy *et al* [124]	17	Male	RT-PCR	Severe	Absence	285/273	Pancreatic loculations	CT	Moderate	Conservative	Alive
65	Berrichi *et al*[125]	36	Female	RT-PCR	Critical	Presence	NA/2570	Diffuse pancreatic enlargement, peripancreatic inflammatory change	CT	Severe	Conservative	Dead
66	Berrichi *et al*[125]	51	Female	RT-PCR	Severe	Presence	NA/676	Diffuse pancreatic enlargement	CT	Mild	Conservative	Alive
67	Kripalani *et al* [126]	79	Female	RT-PCR	Critical	Presence	1075/6178	Diffuse pancreatic enlargement, peripancreatic inflammatory change, acute necrotic pancreatitis	CT	Severe	Cycto-jejunostomy	Alive
68	Narayan *et al* [127]	28	Male	RT-PCR	Critical	Presence	Elevated/elevated	Diffuse pancreatic enlargement, peripancreatic inflammatory change and acute necrotic pancreatitis	CT	Severe	Conservative	Dead
69	Narayan *et al* [127]	45	Female	RT-PCR	Severe	Presence	Elevated/elevated	Peripancreatic inflammatory change	CT	Mild	Conservative	Alive
70	Eldaly *et al*[128]	44	Male	RT-PCR	Non-severe	Presence	773/286	Diffuse pancreatic enlargement	CT	Mild	Conservative	Alive
71	Basukala *et al* [129]	49	Female	RT-PCR	Non-severe	Presence	1563/568	Diffuse pancreatic enlargement, peripancreatic inflammatory change, fluid collection, necrotic pancreatitis	CT	Severe	Gastrocolic ligament and followed by necrotic debridement, and drainage placement	Dead
72	Schembri Higgans *et al*[130]	63	Female	RT-PCR	Non-severe	Presence	1079/NA	After Whipple surgery	CT	Mild	Conservative	Alive
73	Schembri Higgans *et al*[130]	87	Female	RT-PCR	Non-severe	Presence	499/NA	Peripancreatic inflammatory change	CT	Mild	Conservative	Alive
74	Schembri	64	Female	RT-PCR	Non-severe	Presence	2141/NA	Peripancreatic inflammatory change	CT	Mild	Conservative	Alive

	Higgans *et al*[130]											
75	Kopiczko *et al* [131]	6	Female	RT-PCR	Non-severe	Presence	1124/4250	Diffuse pancreatic enlargement, peripancreatic inflammatory change, fluid collection	CT	Mild	Conservative	Alive
76	Kareva *et al*[58]	11	Male	Serological IgG	Non-severe	Presence	489/576	Edematous appendix no change of pancreas	AUS	NA	Conservative	Alive
77	da Costa Ferreira *et al*[132]	35	Male	RT-PCR	Severe	Presence	1669/NA	Diffuse pancreatic enlargement, peripancreatic inflammatory change, fluid collection normal gallbladder and biliary tract	CT	Severe	Conservative	Alive
78	Sánchez-Gollarte *et al*[133]	60	Male	Serological IgG	Severe	Presence	4530/2220	Diffuse pancreatic enlargement, peripancreatic inflammatory change, fluid collection, necrotic pancreatitis	CT	Severe	Drainage of abdominal cavity	Alive
79	Sudarsanam *et al* [134]	35	Male	RT-PCR	Non-severe	Presence	Normal/normal	Peripancreatic inflammatory change, fluid collection, necrotic pancreatitis of tail	CT	NA	Conservative	Alive
80	Faghih Dinevari *et al*[135]	18	Female	RT-PCR	Non-severe	Presence	1288/1541	Diffuse pancreatic enlargement, peripancreatic inflammatory change, fluid collection	CT	Mild	Conservative	Alive
81	Goldstein *et al* [136]	11	Male	Serological IgG	Severe	Presence	1607/2434	Peripancreatic inflammatory change, fluid collection, necrotic pancreatitis	MRI	Moderate	Conservative	Alive
82	Gadiparthi *et al* [137]	74	Female	RT-PCR	Non-severe	Presence	229/7550	Peripancreatic inflammatory change	CT	Mild	Conservative	Alive

RT-PCR: Reverse transcription polymerase chain reaction; IgG: Immunoglobulin G; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; COVID-19: Coronavirus disease 2019; AUS: Abdominal ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging; NA: Not available.

analysis suggested that patients with AP and COVID-19 were frequently men, had idiopathic etiology of AP, a high rate of pancreatic necrosis, higher severity of AP, and serious clinical courses, such as requirement of ICU admission and mechanical ventilation, and high mortality than patients with AP without COVID-19[67]. The prognoses in patients with COVID-19 with AP and those with COVID-19 without AP were different. It remains unclear whether SARS-CoV-2 infections increase AP, as the incidence of AP is rare, but its severity is high when concurrent with COVID-19. An online survey[68] including 22 children with AP and COVID-19 was reported. They were diagnosed as COVID-19 with RT-PCR or detection of SARS-CoV-2 IgG antibodies, while the diagnostic criteria for AP was unavailable. Children aged 10–14 years accounted for 54.5% of all participants in the study. Their clinical courses were serious-60% of them required treatment in the ICU, 45% had multi-organ involvement, 11% had complicated pancreatic necrosis, and 24% developed shock.

The association of AP with SARS-CoV-2 remains unclear, but patients with concurrent AP and COVID-19 show worse prognoses. The fact that some studies reported idiopathic AP during the COVID-19 pandemic indicates existence of COVID-19-attributed AP. Therefore, prospective cohort

studies focused on patients with COVID-19 with idiopathic AP, especially on how to exclude other etiologies of AP, are needed to clarify the COVID-19-attributed AP.

REVIEW OF CASE REPORTS CONTRIBUTED TO CONCURRENT COVID-19 AND AP

Literature search strategy

We identified relevant studies in the literature by searching the PubMed database. The review was restricted to articles published between December 2019 and October 2021, and selected case reports published in English. The search terms were as follows: COVID-19 pancreatitis AND "2019/01/01" (Date-Publication) to "2021/10/31" (Date-Publication) OR SARS-CoV-2 pancreatitis AND "2019/01/01" (Date-Publication) to "2021/10/31" (Date-Publication). We also screened reference lists of selected studies to manually identify relevant studies and include them in the narrative review.

Diagnosis and severity of AP

AP was defined according to diagnostic criteria of the Revised Atlanta Classification[17]. The presence of two out of three features, including abdominal pain consistent with AP, serum lipase activity (or amylase activity) at least three-times greater than the upper normal limit, and characteristic findings of AP on abdominal imaging, was required for the diagnosis of AP.

The severity (mild, moderately severe, and severe) of AP was also defined according to the Revised Atlanta Classification[17].

Diagnosis and severity of COVID-19

The diagnosis of COVID-19 was defined as a positive RT-PCR result or serological test for SARS-CoV-2. The other methods, such as medical history, or chest CT findings, were excluded.

The severity of COVID-19 (mild, moderate, severe, and critical), as classified by the WHO guidelines, was used to stratify patients in the study (https://www.who.int/publications/i/item/clinical-management-of-covid-19). Critical COVID-19 was defined based on the criteria for ARDS, sepsis, septic shock, or other conditions that would normally require life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy. Severe COVID-19 was defined based on any of the following criteria: (1) Oxygen saturation < 90% on room air; (2) Respiratory rate > 30 breaths/min in adults and children aged > 5 years, ≥ 60 breaths/min in children aged < 2 mo, ≥ 50 in children aged 2–11 mo, and ≥ 40 in children aged 1–5 years; and (3) Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest-wall indrawing, grunting, central cyanosis, or presence of any other general danger signs). Non-severe COVID-19 was defined as the absence of any criteria for severe or critical COVID-19.

The data for some cases was insufficient to confirm the severity of COVID-19, but patients who received oxygen therapy were considered to have severe condition. Nevertheless, the indication for oxygen administration varied with institution. However, oxygen saturation < 90%, a criteria for severe COVID-19, was generally used as an indication for oxygen therapy. Additionally, patients who received oxygen therapy generally required hospitalization. Therefore, patients who received oxygen therapy were considered to have severe condition.

Reports included in the review

The literature search of the PubMed database identified 735 studies that met the criteria. We identified eight additional relevant articles in the references of these studies. We excluded 580 non-case study articles, a study in non-English language, three preprints, and an article that could not be reviewed. Of the remaining 158 case studies, 61 were without pancreatic injury or pancreatitis, and thus, were excluded. Moreover, 16 case reports on AP caused by other etiologies, such as biliary disease, alcohol, acute on chronic pancreatitis, hypertriglyceridemia, cytomegalovirus infection, methanol, lymphoma, and vaccination were excluded. In the remaining 81 case studies, six studies comprised eight cases that were not confirmed for AP based on the Revised Atlanta Classification. Two case studies did not include objective data for COVID-19 diagnosis. After removing these studies, 73 studies that included eight case series and 65 case reports were finally assessed in this review. In three of eight case series, one patient without pancreatitis (but with acute cholecystitis), two with negative RT-PCR test, and eight without RT-PCR test or serological IgG for SARS-CoV-2 were excluded. Eighty-two cases of suspected COVID-19-attributed AP were evaluated. Four of 82 cases were RT-PCR negative, but were serological IgG positive for SARS-CoV-2. However, these studies had a limitation that the etiological search for AP was insufficient in almost all cases. Therefore, we classified the potential of other etiologies for AP as-probable, improbable, and uncertain-for each case. The definition of "probable" for each etiology was as follows: Alcoholic AP, consuming ≥ 60 g of ethanol every day before AP onset; biliary AP, gallstones or biliary tract dilation on the abdominal image findings at AP onset (regarded as biliary AP when any serological hepatobiliary test results exceeded more than three-times the upper normal limit unless endoscopic ultrasonography or ERCP excluded any biliary diseases); hypertriglyceridemia, fasting

triglycerides > 1000 mg/dL (11.3 mmol/L) at AP onset[19]; hypercalcemia, serological calcium > 10.4 mg/dL (2.60 mmol/L) at AP onset; drug-induced AP, new medication within one month before AP onset; acute aggravation on chronic pancreatitis, chronic pancreatitis existed, such as pancreatic calcification, before AP onset; infections, positive serological diagnosis for pathogens at AP onset; ischemia/reperfusion, episodes of hypoxic or hypovolemic status, *i.e.*, cardiopulmonary arrest, shock, or mechanical ventilation, before pancreatitis onset; and trauma/anatomy, history of abdominal trauma or upper abdominal surgery with reconstruction of the gastrointestinal tract. In children, genetic AP was defined as existence of a family history of AP, *i.e.*, ≥ 2 first-degree relatives (or ≥ 3 s-degree relatives) to have unexplained recurrent acute or chronic pancreatitis in ≥ 2 generations[69]. Moreover, in cases aged 0–19 years, MIS-C/PIMS-induced AP was also evaluated. The MIS-C/PIMS was defined according to the WHO definition (https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19). In case of insufficient etiological information, the probability of AP was regarded as uncertain.

Reports results

The characteristics of patients with COVID-19-attributed AP are shown in Tables 1–3. The probability of other etiologies for AP in included cases were as follows-alcohol: 0 probable, 64 improbable, and 18 uncertain; biliary AP: 8, 59, and 15; hypertriglyceridemia: 1, 54, and 27; hypercalcemia: 0, 40, and 42; drug-induced AP: 17, 58, and 17; acute aggravation on chronic pancreatitis: 1, 81, and 0; infections: 0, 7, and 75; ischemia/reperfusion: 10, 68, and 4; trauma/anatomy: 1, 79, and 2; genetic AP: 0, 7, and 11; and MIS-C/PIMS: 5, 10, and 3, respectively (Table 3 and Figure 2).

The median age at onset of COVID-19-attributed AP was 42.0 (range, 6–87) years. The men-to-women ratio of COVID-19-attributed AP was 37:44. The patient comorbidities were: Hypertension (22 cases), diabetes (15 cases), heart disease (3 cases), respiratory disease (4 cases), obesity (16 cases), renal dysfunction (5 cases), dyslipidemia (4 cases), hyper/hypothyroidism (4 cases), gastroesophageal reflux disease (2 cases), thrombophilia (1 case), thrombosis (1 case), osteoporosis (1 case), anxiety (2 cases), and malignant disease (2 cases). There were 13 patients with histories of abdominal surgeries, including cholecystectomy, hysterectomy, cesarean section, appendectomy, Whipple procedure, small bowel resection, and renal transplantation. Two pregnant women were also included. Almost all patients had no history of alcohol and cigarette abuse. Abdominal pain was the most frequent symptom (91.5%, 75/82), followed by fever (59.8%, 49/78), vomiting (58.5%, 48/79), nausea (47.6%, 39/66), and cough (34.1%, 28/78). None of the patients had any symptoms. The median levels of white blood cells, platelets, D-Dimer, amylase, lipase, lactate dehydrogenase, and C-reactive protein were 13100/μL (range, 3400–230000), 235500/μL (range, 52000–502000), 4.9 μg/mL (range, 0.3–17.7), 635 U/L (range, 47–4530), 895.5 U/L (range, 35.6–11920.0), 366 U/L (range, 170–3553), and 8.5 mg/dL (range, 0.3–59.7), respectively.

The study included 43 patients (55.8%, 43/77) with severe or critical COVID-19. Oxygen therapy for COVID-19 was required in 42 patients (51.2%, 42/69); of those, 19 were treated with mechanical ventilation. Seventeen patients received antiviral therapy with lopinavir/ritonavir, favipiravir, umifenovir, or remdesivir. One of them was treated with both lopinavir/ritonavir and favipiravir. Moreover, two patients received hydroxychloroquine, an antimalarial drug, for treatment of COVID-19. Two cases were treated with tocilizumab, an anti-IL-6 monoclonal antibody, for COVID-19. Corticosteroids were also administered for the treatment of COVID-19 in 21 patients (39.6%, 21/53).

Abdominal images were evaluated in 75 patients, except in two patients as the pancreases could not be visualized *via* abdominal ultrasonography. Two other patients underwent abdominal CT or magnetic resonance imaging, and the findings were consistent with those of pancreatitis-alone, without details. Of the remaining 71 patients, 48 showed peripancreatic inflammatory changes and 33 had peripancreatic fluid collections. Pancreatic enlargement occurred in 42 patients. Pancreatic ischemic changes, such as decreased contrast enhancement in pancreatic parenchyma on abdominal computed tomography was observed in 12 patients (16.9%, 12/71). However, no change was observed in the abdominal image findings in six patients.

In this review, 28 patients were classified as having severe AP (36.8%, 28/76). Almost all patients with AP received conservative therapy, except for four cases. These four patients underwent invasive treatment; of which, one patient with AP and gastric necrosis underwent drainage of the peripancreatic necrotic collections and total gastrectomy, but failed to recover. The other patient received gastrocolic ligament, necrotic debridement, and drainage placement for acute hemorrhagic necrotizing pancreatitis, and died two days after surgery.

The median period of hospitalization for recovering from COVID-19-attributed AP was 8.0 d (range, 2–76). Ten patients (12.7%, 10/79) died due to critical COVID-19 (median hospitalization, 7.0 d; range, 2–22 d).

In summary, patients suspected with COVID-19-attributed AP were relatively young (median age, 42 years), 36.8% of them had severe conditions, and had a high mortality rate (12.7%) similar to that reported in cohort studies and meta-analyses. However, it cannot be ignored that many AP cases reported in these studies may have occurred due to etiologies other than SARS-CoV-2.

Table 3 The probability of other etiologies of acute pancreatitis in cases with coronavirus disease 2019 and acute pancreatitis coexistent

Case No.	Alcohol	Biliary	Hypertrig-lyceride-mia	Drug	Acute aggravati-on on chronic pancreati-tis	Hypercal-cemia	Infection-s	Ischemia/ reperfusi-on	Trauma/ anatomy	Genetics	MIS-C/PIMS
1	N	?	?	Y	N	?	?	N	N	-	-
2	N	N[1]	N	?	N	N	?	Y	N	-	-
3	?	?	N	?	N	N	?	Y	N	-	-
4	N	N	N	N	N	?	?	N	N	-	-
5	N	N	N	N	N	N	N[2]	N	N	-	-
6	N	N	N	N	N	?	?	?	N	-	-
7	N	N	N	N	N	?	?	?	N	-	-
8	N	N	N	N	N	?	?	N	N	-	-
9	N	?	?	N	N	?	?	N	N	?	N
10	?	N	N	N	N	N	?	N	N	-	-
11	N	N	?	Y	N	?	?	N	N	-	-
12	N	N	N	N	N	N	?	N	N	-	-
13	N	N	?	N	N	?	?	N	N	-	-
14	?	Y	?	Y	N	?	?	N	N	-	-
15	N	N	N	Y	N	N	?	N	N	-	-
16	N	N	N	Y	N	N	?	N	N	-	-
17	?	?	N	Y	N	N	?	Y	N	-	-
18	N	N	N	N	N	N	?	N	N	-	-
19	N	N	N	N	N	N	?	N	N	-	-
20	N	N	?	N	N	?	?	N	N	-	-
21	N	N	?	N	N	?	?	N	N	-	-
22	N	N	N	N	N	N	?	N	N	-	-
23	N	N	N	N	N	N	?	N	N	-	-
24	N	N	N	N	N	N	?	N	N	-	-
25	N	N	N	N	N	N	?	N	N	-	-
26	?	N	N	Y	N	N	?	Y	N	-	-
27	N	N	N	N	N	N	?	N	N	-	-
28	N	?	N	N	N	?	?	N	N	N	N
29	N	N	N	N	N	?	?	N	N	N	?
30	N	Y	N	N	Y	?	?	N	N	N	N
31	N	N[1]	?	N	N	?	?	N	N	-	-
32	N	Y	N	N	N	?	?	N	N	?	Y
33	N	N	N	Y	N	N	?	Y	N	-	-
34	N	N	N	N	N	?	?	N	N	-	-
35	N	?	?	?	N	?	?	N	N	-	-
36	N	Y	N	N	N	N	?	Y	N	-	-
37	N	N	?	N	N	?	?	N	N	-	-

38	N	N	N	N	N	N	?	N	N	-	-
39	N	?	?	?	N	?	?	?	?	?	Y
40	N	?	?	?	N	?	?	?	?	?	N
41	N	N	N	Y	N	?	?	Y	N	-	-
42	N	N	N	Y	N	N	?	N	N	-	-
43	N	N	N	N	N	N	N[2]	N	N	-	-
44	N	N	N	Y	N	N	N[2]	Y	N	-	-
45	N	?	?	N	N	?	?	N	N	-	-
46	?	?	?	N	N	N	?	N	N	-	-
47	?	?	?	N	N	?	?	N	N	?	N
48	?	?	?	N	N	?	?	N	N	-	-
49	N	N	N	Y	N	N	?	N	N	-	-
50	N	N	N	Y	N	?	N[2]	N	N	N	Y
51	N	N	?	N	N	?	?	N	N	?	N
52	?	N	N	N	N	?	?	N	N	N	N
53	?	N	N	N	N	N	?	N	N	-	-
54	N	Y	N	N	N	N	?	N	N	-	-
55	N	N	N	N	N	N	?	N	N	-	-
56	N	N	N	N	N	N	?	N	N	-	-
57	N	N	N	?	N	N	?	N	N	-	-
58	N	N	N	N	N	N	?	N	N	-	-
59	N	N	N	N	N	?	?	N	N	-	-
60	N	N	?	N	N	N	?	N	N	N	N
61	N	N	N	N	N	?	?	N	N	?	?
62	N	?	N	Y	N	N	N	Y	N	-	-
63	N	N	N	N	N	?	?	N	N	-	-
64	N	Y	Y	N	N	?	?	N	N	?	?
65	?	N	?	N	N	?	?	N	N	-	-
66	?	N	?	N	N	?	?	N	N	-	-
67	N	N	?	N	N	?	?	N	N	-	-
68	?	N	N	Y	N	?	?	N	N	-	-
69	?	?	?	Y	N	?	?	Y	N	-	-
70	N	N	N	N	N	?	?	N	N	-	-
71	N	N	N	N	N	N	?	N	N	-	-
72	N	N	?	N	N	?	?	N	Y	-	-
73	?	N	N	N	N	?	?	N	N	-	-
74	?	Y	?	N	N	?	?	N	N	-	-
75	N	N	N	N	N	N	N	N	N	?	N
76	N	N	?	N	N	N	?	N	N	?	Y
77	N	Y	N	N	N	N	?	N	N	-	-
78	?	N	?	?	N	N	?	N	N	-	-
79	N	N	N	N	N	N	?	N	N	-	-
80	N	N	N	N	N	N	?	N	N	N	N
81	?	?	?	Y	N	?	N[2]	N	N	?	Y

82	N	N	N	N	N	N	?	N	N	-	-

[1]Serological hepatobiliary test was not shown.
[2]Some infections were denied although others were not.
Y: Probable; N: Improbable; MIS-C: Multisystemic inflammatory syndrome in children; PIMS: Pediatrics inflammatory multisystem syndrome.

CONCLUSION

It remains controversial whether SARS-CoV-2 infections increase AP, but some basic and pathological approaches suggest mechanisms of direct and indirect involvement of the pancreas caused by SARS-CoV-2. Moreover, there are several clinical data to support existence of COVID-19-attributed AP. First, the incidence of idiopathic AP in patients positive for SARS-CoV-2 is higher than that in patients negative for SARS-CoV-2 in some cohorts with concurrent COVID-19 and AP. Second, SARS-CoV-2 infects pancreatic exocrine and endocrine cells as *per* the pathological evaluation of patients deceased due to COVID-19. Moreover, some clinical features of COVID-19-attributed AP, including various etiologies of AP, are revealed, such as a high rate of pancreatic necrosis, higher severity of AP, and serious clinical courses. However, clinical features of COVID-19-attributed AP remain uncertain. A sufficient investigation on etiologies of AP would improve understanding of the clinical features of COVID-19-attributed AP. High-quality clinical studies and case reports that specify the method for differential diagnoses of the other etiologies of AP, including alcohol, biliary, hypertriglyceridemia, hypercalcemia, drugs, ischemia/reperfusion, trauma, infections, and genetic associations need to be evaluated. The present review of case studies suggests criteria to classify the possibility of other etiologies for AP. The criteria may not be appropriate, but the review highlights the insufficient etiological workup of AP, especially for other infections and hypercalcemia. Moreover, in some cases, it is difficult to completely exclude drug-induced and biliary AP from the etiology of AP. These details may be informative for designing future clinical studies.

Several unsolved questions remain, such as the risk factors of AP in patients with COVID-19. It is also uncertain why some patients with COVID-19-attributed AP become severe while others do not. AP may be a rare complication of COVID-19, but some cases develop severe AP attributed to SARS-CoV-2 infection. Thus, the potential of COVID-19-attributed AP should be thoroughly investigated.

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FOOTNOTES

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