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OPINION REVIEW

- 516 Borderline resectable pancreatic cancer: Certainties and controversies
Nappo G, Donisi G, Zerbi A

MINIREVIEWS

- 529 Special surgical approaches during peri-COVID-19 pandemic: Robotic and transanal minimally invasive surgery
Sánchez-Guillén L, Jimenez-Rodriguez RM
- 537 Therapeutic interventional endoscopic ultrasound in pancreato-biliary disorders: Does it really replace the surgical/percutaneous approach?
Lesmana CRA, Paramitha MS, Gani RA
- 548 Association between acute pancreatitis and COVID-19 infection: What do we know?
Jabłońska B, Olakowski M, Mrowiec S

ORIGINAL ARTICLE**Basic Study**

- 563 Efficacy of hybrid endoscopic submucosal dissection with SOUTEN in gastric lesions: An *ex vivo* porcine model basic study
Esaki M, Ihara E, Hashimoto N, Abe S, Aratono C, Shiga N, Sumida Y, Fujii H, Haraguchi K, Takahashi S, Iwasa T, Nakano K, Wada M, Somada S, Nishioka K, Minoda Y, Ogino H, Ogawa Y

SYSTEMATIC REVIEWS

- 574 Acute pancreatitis and COVID-19: A literature review
Correia de Sá T, Soares C, Rocha M
- 585 Chylous ascites in colorectal surgery: A systematic review
Ng ZQ, Han M, Beh HN, Keelan S
- 597 2D vs 3D laparoscopic right colectomy: A propensity score-matching comparison of personal experience with systematic review and meta-analysis
Costa G, Fransvea P, Lepre L, Rondelli F, Costa A, Campanelli M, Lisi G, Mastrangeli MR, Laracca GG, Garbarino GM, Ceccarelli G

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Association between acute pancreatitis and COVID-19 infection: What do we know?

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Abstract

The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also called coronavirus disease 2019 (COVID-19), first originated in Wuhan, China, displaying atypical pneumonia-like respiratory symptoms in affected patients. SARS-CoV-2 primarily attacks the respiratory system, and the most common symptoms include cough, shortness of breath, and fever. However, its impact on the digestive system has been shown, and various clinical gastrointestinal manifestations of this disease have been recognized. Some reports have shown acute pancreatitis (AP) as the initial symptom in patients with COVID-19. AP may be a consequence of direct pancreatic damage by the virus because pancreatic acinar cells contain angiotensin-converting enzyme 2 receptor proteins, and SARS-CoV-2 can bind to these receptors, causing pancreatic injury. Moreover, AP may be a secondary indicator of cytokine storms and altered inflammatory responses. Our review of the literature shows that SARS-CoV-2 appears to be a new etiological infectious factor related to AP. In this manuscript, a comprehensive review of case reports and case series of patients with AP and COVID-19 is presented. All reports on COVID-19-associated AP are summarized. All cases are thoroughly analyzed and discussed in-depth.

Key Words: SARS-CoV-2; COVID-19; Acute pancreatitis; Angiotensin-converting enzyme 2

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Core Tip: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears to be a new etiological infectious factor of acute pancreatitis (AP). AP in coronavirus disease 2019 (COVID-19) patients may be caused by direct attack of SARS-CoV-2 to pancreatic acinar cells or indirect, uncontrollable systemic inflammatory response from

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cytokine storm syndrome leading to multi-organ dysfunction including pancreatic injury or locoregional vasculitis and thrombotic microangiopathy from COVID-19. To our knowledge, there is no such comprehensive review with a detailed description of various articles on this topic including case reports and cohort studies.

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INTRODUCTION

The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), first originated in Wuhan, China, and manifested atypical pneumonia-like respiratory symptoms in affected patients. It has spread all over the world and has been described as a pandemic on March 11, 2020 by the World Health Organization. SARS-CoV-2 is a zoonotic virus which is most commonly observed in bats. At the beginning, it involves the respiratory system, very similar to SARS-CoV and Middle East respiratory syndrome coronavirus, but with a significantly higher rate of spreading. The number of cases of COVID-19 is still increasing, with > 105 million cases and > 2 million deaths as of February 5, 2020[1,2].

At the beginning, SARS-CoV-2 involves the respiratory system, with cough, shortness of breath, diminishment of taste, absence of smell, and fever being the most common clinical symptoms. The influence of this virus on the alimentary system has been noted, and various clinical gastrointestinal signs of this disease have been recognized[1,2].

According to Fang *et al*[3]'s report from Wuhan, in about 79% of patients, various gastrointestinal symptoms (diarrhea, decreased appetite, nausea, vomiting, abdominal pain, and gastrointestinal bleeding) were observed. These symptoms were present at the disease beginning and they were followed by subsequent hospitalization. Although the prevalence of these symptoms in Wuhan was high, according to the first research regarding the manifestation of COVID-19, diarrhea was present in only 3% of patients[3]. In Tian *et al*[4]'s study, anorexia was the most frequent gastrointestinal symptom, observed in 39.9%-50.2% of adults, while diarrhea was the most frequent manifestation in both adults and children (2%-49.5%), and vomiting was more frequent in pediatric patients. Vomiting was reported in 3.6%-15.9% of adults and in 6.5%-66.7% of pediatric patients. Nausea occurred in 1%-29.4% of patients, gastrointestinal hemorrhage was noted in 4%-13.7%, and abdominal pain (2.2%-6.0%) was more frequent in patients in a severe clinical condition[4]. In Cheung *et al*[5]'s meta-analysis, there were 18 studies on loss of appetite, 32 on nausea or/and vomiting, 58 on diarrhea, and 12 on abdominal pain. In that study, the pooled incidence of loss of appetite, nausea/vomiting, diarrhea, and abdominal pain/ discomfort was 26.8% [95% confidence interval (CI): 16.2-40.8], 10.2% (95%CI: 6.6-15.3), 12.5% (95%CI: 9.6-16.0), and 9.2% (95%CI: 5.7-14.5), respectively[5]. Moreover, SARS-CoV-2 RNA has been identified in the gastrointestinal tract by numerous authors[5-8].

Various case reports have described acute pancreatitis (AP) as the initial manifestation in patients with COVID-19[9-12]. According to numerous authors, pancreatic acinar cells have angiotensin-converting enzyme 2 (ACE2) receptor proteins, and SARS-CoV-2 can bind to these receptors and lead to pancreatic injury[9,13,14].

PATHOGENESIS OF PANCREATIC INJURY DURING COVID-19

In July 2020, Wang *et al*[14] first described pancreatic injury in COVID-19. According to the authors, the SARS-CoV-2 ACE2 receptor was highly expressed in pancreatic islets, and SARS-CoV-2 infection led to the injury of the islets and acute diabetes. In that study of nine patients with COVID-19 with pancreatic injury, abnormal blood glucose levels were found in six patients. These results suggest that pancreatic injury in COVID-19 could be caused directly by the cytopathic effect mediated by local SARS-CoV-2 replication. On the other hand, pancreatic injury can be caused indirectly by

systemic responses to respiratory failure or the altered immune response induced by SARS-CoV-2 infection, which also leads to multiple organ injury. In the above-mentioned study, heart, liver, and renal injuries were noted simultaneously. Moreover, antipyretic drugs have been taken by most patients before admission, which could also lead to drug-related pancreatic injury[14].

In December 2020, Samanta *et al*[15] published an interesting article in which the authors explained precisely the multiorgan tropism of SARS-CoV-2. It attaches to the ACE2 receptor on lung type 2 alveolar cells, which leads to lung injury. Once the spike (S) protein attaches to alveolar cells, it leads to a cytokine storm that deteriorates the alveolar epithelium, hindering oxygen exchange and manifesting as acute respiratory distress syndrome (ARDS)[15,16]. Crucially, ACE2 receptor expression is present not only in the lungs but also in esophageal epithelial cells, ileal and colonic enterocytes, and cardiovascular, renal, and pancreatic tissues. Moreover, the mRNA levels of ACE2 have been found to be higher in the pancreas than in the lung[15]. ACE2 expression is noted both in the exocrine and endocrine pancreatic tissues[15,17]. The S protein engages ACE2 as the entry receptor. Additionally, cell entry is facilitated by priming of the S protein by transmembrane protease serine 2 (TMPRSS2) or other proteases. Combined expression of both ACE2 and TMPRSS2 is needed for successful viral entry into a cell[15,18]. Binding of the virus to the ACE2 receptor leads to pancreatic injury. Altered immune response and cytokine storm have been observed in severe COVID-19, with higher levels of interleukin-6 associated with a worse prognosis. It has been observed that pancreatic injury was greater in severe compared to mild COVID-19 disease, which was probably caused by the cytokine storm and immune alteration[15].

CASE REPORTS AND COHORT STUDIES ON AP IN COVID-19 IN THE LITERATURE SEARCH

Methods of literature search

We searched the PubMed database. The search terms and MeSH headings were as follows: “SARS-CoV-2” or “COVID-19”, and “acute pancreatitis”. Selected articles, including case reports and cohort studies as well as letters to the editor and reviews related to the topic of our paper, were read, analyzed, discussed, and cited. The articles are presented and reviewed chronologically according to the publication date. Full-text English language articles were included in our review when they met the criteria as follows:

Population: Adults with AP and COVID-19 were included, and the pediatric population was not analyzed.

Outcomes of interest: Age, sex, timing of AP related to COVID-19, clinical manifestation, patient medical history, laboratory and imaging diagnostics, management, disease course, and prognosis.

A summary of cited case reports and cohort studies is presented in Tables 1 and 2.

Results of the literature search

Hadi *et al*[6] published an online description of three cases of AP in COVID-19 patients. The authors described three family members (a 47-year-old daughter, a 68-year-old mother, and a 71-year-old father) admitted with COVID-19 to the intensive care unit (ICU) in March 2020. In two of them, AP associated with SARS-CoV-2 was reported. Other causes of AP were ruled out in the daughter and the mother. In all patients, different gastrointestinal symptoms were present. All patients were hospitalized in the ICU. The two cases described in that paper were characterized by severe AP, leading to multiorgan failure (MOF), including adult respiratory distress and kidney failure. The father was admitted to the ICU due to COVID-19 induced respiratory failure and gastrointestinal symptoms, but in him AP was not confirmed [6].

Aloysius *et al*[10] described the case of a 36-year-old obese [body mass index (BMI) = 35] Hispanic woman with fever, dry cough, increasing dyspnea, nausea, vomiting, and diarrhea for 8 d, and epigastric pain radiating to the back for 2 d. The patient was diagnosed with severe AP with ARDS, and she was admitted to the ICU. At the beginning, she was treated symptomatically using conservative management (zero diet, intravenous fluids, analgesics, and empiric antibiotics as the prevention of bacterial pneumonia). Later, oxygen supplementation was used due to respiratory failure. The gastrointestinal and respiratory symptoms resolved following 2 wk of the

Table 1 Summary of case reports on acute pancreatitis and coronavirus disease 2019

Ref.	Type of study	Age (yr)/gender	Period from COVID-19 onset to AP	AP severity	Treatment method	Prognosis
Anand <i>et al</i> [20]	Case report	59 F	10 d	MAP	Conservative	Recovery
Hadi <i>et al</i> [6]	Case report	47 F	Several days	SAP	Conservative	ICU hospital
		58 F	Several days	SAP	Conservative	ICU hospital
Aloysius <i>et al</i> [10]	Case report	36 F	6 d	SAP	ICU, conservative	Recovery
Gadiparthi <i>et al</i> [19]	Case report	40 M	AP 3 d before (+) PCR	SAP	ICU, Conservative	Recovery
Miao <i>et al</i> [21]	Case report	26 F	AP 7 d before (+) PCR	MAP	Conservative	Recovery
Schepis <i>et al</i> [22]	Case report	67 F	MAP “recently” before (+) PCR	NA	Cyst drainage	Recovery
Meireles <i>et al</i> [23]	Case report	36 F	11 d	MAP	Conservative	Recovery
Pinte <i>et al</i> [24]	Case report	47 M	19 d	MAP	Conservative	Recovery
Karimzadeh <i>et al</i> [12]	Case report	65 F	AP 3 d before (+) PCR	MAP	ICU, conservative	Recovery
Wang <i>et al</i> [25]	Case report	42 M	AP 8 d before (+) PCR	MAP	ICU, conservative	Death
		35 M	AP 11 d before (+) PCR	MAP	Conservative	Recovery
Brikman <i>et al</i> [28]	Case report	61 M	14 d	MAP	Conservative	Recovery
Purayil <i>et al</i> [29]	Case report	58 M	AP 3 d before (+) PCR	MAP	Conservative	Recovery
Lakshmanan <i>et al</i> [30]	Case report	68 M	Several days	MAP	Conservative	Recovery
Bokhari <i>et al</i> [31]	Case report	32 M	7 d	MAP	Conservative	Recovery
Kumaran <i>et al</i> [32]	Case report	67 F	0 d	SAP	ICU, conservative	Recovery
Alves <i>et al</i> [33]	Case report	56 F	Several days	SAP	ICU, conservative	Recovery
Kurihara <i>et al</i> [34]	Case report	55 F	14 d	MAP	ICU, conservative	Recovery
Simou <i>et al</i> [2]	Case report	67 M	23 d	SAP	ICU, conservative	Death
Acherjya <i>et al</i> [35]	Case report	57 F	9 d	MSAP	Conservative	Recovery
Shinohara <i>et al</i> [36]	Case report	58 M	10 d	MAP	Conservative	Recovery
Meyers <i>et al</i> [37]	Case report	67 M	AP 2 d before PCR (+)	MAP	Conservative	Recovery
Zielecki <i>et al</i> [38]	Case report	38 M	AP 14 d before PCR (+)	SAP	Conservative	Recovery
Patnaik <i>et al</i> [39]	Case report	29 M	AP 5 d before PCR (+)	MAP	Conservative	Recovery
Rabice <i>et al</i> [40]	Case report	36 FP	5 d	MAP	Conservative	Recovery
Mazrouei <i>et al</i> [41]	Case report	24 M	AP 2 d before PCR (+)	MAP	Conservative	Recovery
Kandasamy <i>et al</i> [42]	Case report	46 F	AP 2 d before PCR (+)	MSAP	Conservative	Recovery
Tollard <i>et al</i> [44]	Case report	32 F	2 d	SAP	ICU, conservative	Death
Alwaeli <i>et al</i> [45]	Case report	20 M	AP 2 d before PCR (+)	MAP	ICU, conservative	Recovery
Narang <i>et al</i> [46]	Case report	20 FP	5 d	MAP	ICU, conservative	Recovery
Jespersen Nizamic <i>et al</i> [49]	Case report	49 F	9 d	MAP	Conservative	Recovery
Cheung <i>et al</i> [50]	Case report	38 M	7 d	MAP	Conservative	Recovery

F: Female; M: Male; COVID-19: Coronavirus disease 2019; AP: Acute pancreatitis; PCR: Polymerase chain reaction; NA: Not applicable; MAP: Mild acute pancreatitis; SAP: Severe acute pancreatitis; MSAP: Moderate severe acute pancreatitis; ICU: Intensive care unit.

above-mentioned therapy[10].

Gadiparthi *et al*[19] reported the case of a 40-year-old obese (BMI = 38.8 kg/m²) man with severe epigastric pain radiating to the back for 2 d and elevated serum lipase and triglyceride in laboratory tests. Abdominal computed tomography (CT) showed extensive peripancreatic inflammation and fluid around and AP was diagnosed. The

Table 2 Summary of cohort studies on acute pancreatitis and coronavirus disease 2019

Ref.	Type of study	Design of study and conclusions
Wang <i>et al</i> [14]	Cohort study	9/52 pancreatic injury/COVID patients (6 M, 3 F; mean age 55 (25-71), PCR on admission, retrospective study A higher incidence of loss of appetite, diarrhea, and more severe illness on admission in patients with pancreatic injury
Dirweesh <i>et al</i> [27]	Cohort study	Comparison of 14 COVID (+) and 61 COVID (-) AP, retrospective multicenter study A higher Charlson Comorbidity Index, mortality, MOF in COVID (+), comparable age, sex, infected necrosis, venous thrombosis, endocrine insufficiency
Akarsu <i>et al</i> [43]	Cohort study	Comparison of 40 COVID-AP (+) and 285 COVID AP (-), prospective study Higher hospitalization, mortality rate, and CRP in COVID AP+; D-dimer and PCT were comparable in both groups
Miró <i>et al</i> [47]	Cohort study	Comparison of COVID-AP, COVID non-AP and non-COVID AP; Retrospective study (62 Spanish EDs) Comparable mortality in COVID-AP and COVID-non-AP, higher mortality in COVID-AP than in non-COVID-AP, and higher AP severity in COVID patients
Inamdar <i>et al</i> [9]	Cohort study	Comparison 32 COVID-AP and 157 non-COVID AP, retrospective study Charlson Comorbidity Index, age, sex, pancreatic necrosis, mortality rate comparable in both groups, a higher hospitalization, mechanical ventilation in COVID-AP, “idiopathic pancreatitis” more frequent in COVID-positive patients (69% vs 21%)
Gubatan <i>et al</i> [48]	Cohort study	Analysis of COVID among patients with pancreatitis history, retrospective study Comparison of COVID and non-COVID patients with prior pancreatitis, “idiopathic” pancreatitis more frequent in COVID group; higher age, male prevalence, Asian ethnicity in COVID patients
Szatmary <i>et al</i> [51]	Cohort study	Cohort of 5 AP/COVID patients, retrospective study

F: Female; M: Male; COVID: Coronavirus disease; AP: Acute pancreatitis; PCR: Polymerase chain reaction; MOF: Multiorgan failure; CRP: C-reactive protein; PCT: Procalcitonin; ED: Emergency departments; PI: Pancreatic injury.

patient was hospitalized in the ICU, and intravenous insulin therapy was used. On day 1 in the ICU, a fever and acute respiratory failure were observed in this patient and supplemental oxygen therapy was needed. Then, COVID-19 was confirmed. On hospital day 6, he was discharged in stable condition[19].

Anand *et al*[20] reported the case of a 59-year-old woman with COVID-19 [confirmed by reverse transcriptase polymerase chain reaction (RT-PCR)] and symptoms of AP. Cholecystectomy and thrombophilia were reported in her medical history. At the beginning, she was admitted to the emergency department (ED) with fever, cough, sore throat, and myalgia. Intravenous vancomycin for streptococcal pneumonia complicated with COVID-19 was administered. She was discharged on day 5 with continuation of doxycycline. After 5 d, she was readmitted due to fever, abdominal pain, constipation, and increased C-reactive protein and white blood cell counts in laboratory results. CT performed on day 3 showed pancreatic and peripancreatic edema (the pancreas was atrophic previously). AP was diagnosed. Conservative treatment was used and the patient was discharged after 7 d[20].

Miao *et al*[21] described the case of a previously healthy 26-year-old woman with a 1-wk history of severe vomiting, epigastric pain, and fever and increased lipase levels in blood tests. Abdominal CT performed at day 1 (day 7 from the onset) showed pancreatic edema. The patient was discharged in good general condition following 7 d of conservative treatment[21].

In July 2020, Schepis *et al*[22] reported the case of a 67-year-old woman with fever, epigastric pain, and vomiting, after a recent hospitalization due to interstitial edematous AP of unknown origin. A large pancreatic pseudocyst (16 cm × 8 cm × 12 cm) impressing the stomach and “ground glass” opacities typical for COVID-19 pneumonia were shown in CT. Endoscopic ultrasound-guided transgastric drainage of the pseudocyst using the AXIOS Stent and Electrocautery Enhanced Delivery System was successfully performed. The cyst fluid was taken for laboratory tests. PCR showed SARS-CoV-2 RNA in the pseudocyst sample. It was the first qualitative and

quantitative detection of SARS-CoV-2 RNA in the fluid of a pancreatic collection in the literature. Based on this study, the authors presented three hypotheses for SARS-CoV-2 pancreatic disease: (1) SARS-CoV-2 can have a tropism for pancreatic cells, leading to a direct cytopathic effect; (2) The presence of SARS-CoV-2 in the pancreatic collection can be secondary using other cells (*e.g.*, inflammatory cells) as Trojan horses; or (3) It can be a result of retrograde contamination from the gastrointestinal tract[22].

Meireles *et al*[23] described the case of a 36-year-old black woman with SARS-CoV-2 pneumonia, with dry cough, breathlessness, and fever for 4 d. During supplemental oxygen therapy for pneumonia, on day 7 (day 11 of disease), nausea, vomiting, and epigastric pain were reported, with no fever or other physical signs but with increased levels of amylase and lipase in blood tests. Supportive therapy was used, and clinical, laboratory, and radiological improvement was achieved (with no pancreatic pathology in CT on day 3)[23].

Pinte *et al*[24] reported the case of a 47-year-old male patient with COVID-19 without significant medical history and with only dry cough for a week. On day 12, he complained of severe epigastric pain radiating to the back, nausea, constipation, and lack of flatus. CT showed scattered bilateral subpleural ground glass opacities, edematous lesions in the caudal region of the pancreas, and bowel distention without evidence of obstruction. According to the modified Atlanta criteria, the patient was diagnosed with AP complicated by ileus[24].

Karimzadeh *et al*[12] described a 65-year-old woman with epigastric pain, nausea, chills, and myalgia for 5 d. On day 2, mild shortness of breath developed. Chest CT revealed bilateral subpleural patchy consolidation and ground glass opacities. The patient was hospitalized in the ICU and received supplemental oxygen. On day 5, amylase and lipase levels increased. Chest CT revealed COVID-19 pneumonia, while abdominal CT reported no abnormalities. Intravenous and oral treatment (antiviral drugs and antibiotics), oxygenation, and supportive care were used. She was discharged in good clinical condition after 18 d[12].

In September 2020, Wang *et al*[25] reported the first two cases of COVID-19-induced AP. The authors described two cases of COVID-19 with AP as the initial manifestation in Wuhan, China. The first patient (a 42-year-old man with nausea and epigastric pain radiating to the back for 3 d) died despite maximal mechanical ventilatory support and circulation support, while the second patient (a 35-year-old man with epigastric pain radiating to the back, nausea, and vomiting) was finally improved and discharged. In the first patient, somatostatin, proton pump inhibitors, and fluids were administered. Then, chest discomfort and dyspnea were reported. Chest CT on day 4 showed bilateral lung multiple ground-glass opacities. Arbidol therapy and oxygenation were used. However, his dyspnea worsened. On day 6, sudden cardiac arrest was reported. Cardiopulmonary resuscitation, tracheal intubation, sedation therapy, and mechanical ventilation were administered. Then, he was admitted to the ICU, and continuous renal replacement therapy (CRRT) was started on day 9 due to acute renal failure. Despite intensive therapy, the patient died on day 10. In the second patient, enteral nutrition, somatostatin, proton pump inhibitors, arbidol, and fluids were used. Abdominal CT (on day 6 of disease) showed pancreatic and peripancreatic edema and fluid and prerenal fascial thickening without biliary dilatation or microlithiasis. Following the treatment, his condition improved and he was discharged. The authors noted that the number of T lymphocytes in the peripheral blood was decreased in these two patients. A decreased count of T lymphocytes is common in severe COVID-19, indicating that this coronavirus can commonly attack T lymphocytes. The T-cell count was extremely low in the first patient after SARS-CoV-2 infection, and the patient died despite maximal mechanical ventilatory support circulation supports. According to the authors, a low T-cell count may be a poor prognostic factor in COVID-19 patients[25].

Wang *et al*[14] reported 52 patients with COVID-19 pneumonia admitted to Zhongnan Hospital of Wuhan University from January 20 to February 28, 2020. Pancreatic injury was defined as any abnormality in amylase (normal range, 0-90 U/L) or lipase (normal range, 0-70 U/L). Among the 52 patients with COVID-19 pneumonia, the incidence of various organ injuries was as follows: Heart injury, 33% (abnormal lactate dehydrogenase or creatine kinase levels); liver injury, 29% (abnormal aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase, or alkaline phosphatase levels); pancreatic injury, 17%; renal injury, 8% (abnormal creatinine level); and diarrhea, 2%. The mean age of the nine patients with pancreatic injury was 55 (range 25 to 71) years. In five of these patients, the following comorbidities were reported: Hypertension, diabetes, and heart disease. Fever and respiratory complaints were the common symptoms[14]. Four patients were categorized as having serious illness on admission. The median duration of SARS-

CoV-2 negative test was 22 d from symptom onset. In COVID-19 patients without pancreatic injury, a higher incidence of loss of appetite and diarrhea, more severe illness on admission, lower levels of CD3⁺ and CD4⁺ T cells, and higher levels of aspartate aminotransferase, γ -glutamyltransferase, creatinine, lactate dehydrogenase, and erythrocyte sedimentation rate was reported compared to those without pancreatic injury. There were no significant differences in corticosteroid treatment, mechanical ventilation, or viral negative conversion time between the two groups[14].

According to Chiarello *et al*[26], AP with concomitant COVID-19 can be associated with a worse prognosis due to a double pulmonary injury (directly by a virus, and indirectly by cytokine storm secondary to AP). The authors noted that in severe AP, lung involvement was common, and it could lead to severe ARDS. On the other hand, COVID-19 pneumonia can worsen lung injury and ARDS due to AP. The authors suggested that during the COVID-19 pandemic, CT scans should be routinely extended to the chest. In the authors' opinion, an early chest CT scan allows the differentiation of pulmonary disease secondary to viral infection from ARDS caused by AP. In COVID-19 pneumonia, a ground-glass sign is common, as pleural effusion and alveolar involvement are later radiological signs. In COVID-19 disease, there are segmentary micro-embolisms that are not present in ARDS[26].

Dirweesh *et al*[27] compared patients with AP according to SARS-CoV-2 status in a retrospective analysis of patients treated between March 1 and June 30, 2020. The analysis involved patients from seven hospitals in Minnesota during a 4-mo period. Out of 339 patients with AP treated during the study period, 75 (22%) with documented PCR testing for SARS-CoV-2 were included, of whom 14 (18.7%) tested positive for COVID-19. Age (48.4 ± 14.1 years *vs* 55.2 ± 14.8 years, $P = 0.76$), sex ($P = 0.77$), ethnicity ($P = 0.77$), and BMI ($P = 0.95$) were comparable in the COVID-19-positive and COVID-19-negative patients. In COVID-19-positive AP patients, higher Charlson Comorbidity Index ($P = 0.003$) and BISAP scores ($P < 0.0001$) were noted. Alcoholic AP and idiopathic AP were the most common in the COVID-19-negative and COVID-19-positive cohorts, respectively ($P < 0.0001$). Mortality was significantly higher in COVID-19-positive patients with AP ($P = 0.004$). Also, MOF ($P < 0.0001$) and persistent organ failure ($P < 0.0001$) were more common in these patients. The AP pattern ($P = 0.63$), frequency of infected necrosis ($P = 0.74$), splanchnic venous thrombosis ($P = 0.3$), and acute endocrine insufficiency ($P > 0.99$) were similar in the two groups. Length of hospital stay was comparable in the two groups (10.8 ± 7.2 d *vs* 6.5 ± 6.7 d, $P = 0.67$). Based on these results, the authors concluded that the complex interaction between AP and COVID-19 is associated with a higher risk of MOF, morbidity, and mortality in patients[27].

Brikman *et al*[28] reported the case of a 61-year-old man with fever, dyspnea, and cough for 5 d. After 3 d from admission, severe COVID-19 pneumonia developed. Typical anti-COVID-19 treatment was administered. On day 14, sudden diffuse abdominal pain, anorexia, leukocytosis, and increased lipase levels were noted. Abdominal CT showed signs of pancreatitis. AP was diagnosed, and supportive treatment, including intravenous fluids and analgesia, was applied. The patient's clinical condition improved after 2 d of conservative treatment[28].

Purayil *et al*[29] reported the case of a 58-year-old male patient with fever, vomiting, and epigastric pain for 3 d, without diarrhea or respiratory symptoms and with increased amylase and lipase levels in blood tests. Chest CT revealed COVID-19 pneumonia. On ultrasound, the pancreas was not visible. His clinical condition improved after conservative treatment[29].

Lakshmanan *et al*[30] reported the case of a 68-year-old man with pneumonia and AP manifesting with nausea, vomiting, and anorexia, without abdominal pain, with increased amylase and lipase levels in laboratory results. Abdominal CT showed pancreatic and peripancreatic inflammation typical for AP. Conservative treatment (intravenous fluids, analgesics, antibiotics, and antiemetics) was used. After 7 d of treatment, he was discharged in good clinical condition[30].

Bokhari *et al*[31] described the case of a 32-year-old man with severe abdominal pain, fever, and vomiting 1 wk after COVID-19 diagnosis. Laboratory and radiological investigations revealed a diagnosis of AP. He underwent conservative management using intravenous fluids, analgesics, antibiotics, and antiemetics and was discharged after 3 d in good general condition[31].

Kumaran *et al*[32] described the case of a 67-year-old woman with a 1-d history of epigastric pain, diarrhea, and vomiting, a year after previous laparotomy and small intestine resection due to superior mesenteric artery stenosis. Apixaban was used due to her previous thrombotic complication. CT performed at admission revealed extensive peripancreatic fluid collection without necrosis. The patient's clinical status deteriorated and angio-CT was performed, which revealed necrotizing pancreatitis.

The patient was hospitalized initially in the surgical units and later in the ICU due to deterioration of vital signs. She was managed conservatively with intravenous fluids and intravenous antibiotics. Surgical treatment was not needed[32].

Alves *et al*[33] described the case of a 56-year-old woman with dry cough, dyspnea, general malaise, and epigastric pain for several days. CT showed COVID-19 pneumonia and pancreatic abnormalities such as tail parenchymal enlargement and surrounding retroperitoneal fat stranding. In addition, amylase and lipase levels were elevated. According to the Modified Glasgow Acute Pancreatitis Score (3 points), severe AP was diagnosed, but with no complication. Supportive therapy (intravenous fluids and a bland diet) was used. The patient was discharged after 35 d of hospitalization in good general condition[33].

Kurihara *et al*[34] described the case of a 55-year-old patient with fever and cough for 1 wk. The patient was intubated for severe respiratory distress using lung-protective mechanical ventilatory strategies, and percutaneous veno-venous extracorporeal membrane oxygenation support was used. Additionally, intravenous antibiotics (meropenem and vancomycin), an oral antiviral agent (favipiravir), and CRRT for acute kidney injury were administered. On day 14, blood tests showed elevated pancreatic enzymes. The patient was unable to describe any abdominal pain because of sedation. AP was suspected, and an ultrasonographic examination was performed. Ultrasonography revealed no pancreatic duct dilation, tumor in the pancreas, or bile duct stones. On day 23, CT showed diffuse parenchymal enlargement and stranding of the surrounding retroperitoneal fat, and AP was diagnosed. The patient was discharged following 40 d of intensive treatment[34].

Simou *et al*[2] described the case of a 67-year-old patient with a history of type 2 diabetes treated with oral antidiabetics who had undergone a cholecystectomy 10 years previously, with obesity (BMI of 34 kg/m²), fever, dyspnea, myalgia, and arthralgia without associated abdominal signs persisting for 10 d. COVID-19 pneumonia with pulmonary failure was recognized and typical treatments were administered, including oxygen therapy, hydroxychloroquine, azithromycin, methylprednisolone, vitamin C1, zinc, and low molecular weight heparin. On day 5, the patient's condition was deteriorated and sepsis developed. On the 13th day, a CT scan demonstrated acute stage C pancreatitis according to the Balthazar classification. Lipasemia was detected in blood tests. Despite intensive therapy, the patient had an unfavorable outcome and died on day 18[2].

Acherjya *et al*[35] reported the case of a 57-year-old female physician with breast and larynx cancers, with fever, generalized body pain, fatigue, arthralgia, and loss of smell for 2 d. She was treated for COVID-19 pneumonia (favipiravir, prophylactic dose of enoxaparin, and oxygen inhalation). On day 5 after symptom onset, her oxygen saturation decreased to 87%. On days 6 and 9, severe epigastric pain radiating to the back and vomiting were noted. Hyperlipasemia was present, and abdominal CT showed a moderately swollen pancreas. Therefore, AP was recognized and conservatively treated (zero diet, intravenous fluids, intravenous broad-spectrum antibiotics, omeprazole, and pethidine hydrochloride). She was discharged in good general condition following 14 d without any pancreatitis-related complications[35].

Shinohara *et al*[36] described the case of a 58-year-old Japanese man with fever and increasing dyspnea for 7 d. He was hospitalized due to COVID-19 pneumonia. The first CT did not show abnormalities in the pancreas. The patient's condition deteriorated, and endotracheal intubation was performed. Treatment with piperacillin-tazobactam, azithromycin, and a combination of favipiravir and nafamostat mesilate was initiated. On day 3 of hospitalization, the patient developed abdominal pain and fever, and the patient's serum pancreatic amylase increased. The second abdominal CT revealed diffuse enlargement of the pancreas with peripancreatic fat stranding indicating AP. He was discharged in stable condition on day 30 of hospitalization. According to the authors, it is possible that their patient developed AP from other etiologies, considering drug-induced pancreatitis caused by favipiravir and nafamostat mesilate[36].

Meyers *et al*[37] reported the case of a 67-year-old man with prior cholecystectomy (2015) and a history of alcohol use after 1 d of acute onset epigastric abdominal discomfort, with no cough, fevers, or other gastrointestinal symptoms. Additionally, hyperlipasemia was present. A CT scan demonstrated acute interstitial edematous pancreatitis with moderate peripancreatic stranding and edema. The patient was diagnosed with AP possibly secondary to recent alcohol use (last consumption 2 beers 6 d prior to admission, occasional use otherwise) and treated with intravenous analgesics, antiemetics, and aggressive fluid resuscitation. Two days after COVID-19 pneumonia, PCR and CT were performed. In the discussion, the authors wrote that in their patient with light alcohol use 6 d before symptom onset, alcohol was an

unconvincing etiology, and COVID-19 etiology was the most likely[37].

Zielecki *et al*[38] reported the case of a 38-year-old man with late edematous moderate AP, liver steatosis, hepatosplenomegaly, alcohol abuse, and confirmed COVID-19. He had previously been hospitalized for 2 wk in another medical center due to severe AP presenting with acute-onset upper abdominal pain, metabolic acidosis, and features of MOF. On CT, necrosis of > 50% of the pancreas (body and tail), peripancreatic fluid accumulation and fluid accumulation along Gerota's fascia, acute necrosis collection, and COVID-19 pneumonia were detected. Intensive conservative treatment was administered, including wide-spectrum antibiotics, parenteral nutrition, and tocilizumab. On day 15, the patient was discharged in good clinical condition[38].

Patnaik *et al*[39] described the case of a 29-year-old man with abdominal pain radiating to the back and dyspnea for 5 d. Laboratory tests revealed leukocytosis, hyperamylasemia, and hyperlipasemia. CT showed that the pancreas was swollen. AP was diagnosed. Conservative treatment using meropenem was administered. After several days, his clinical state was improved, and he was discharged[39].

Rabice *et al*[40] described a 36-year-old pregnant woman with nausea, vomiting, and abdominal pain in the course of COVID-19. Laboratory tests showed hyperamylasemia and hypertriglyceridemia. She was diagnosed with AP. Her clinical condition was improved after conservative treatment and cesarean section[40].

Mazrouei *et al*[41] described a 24-year-old man with nonradiating severe epigastric pain, nausea, and vomiting for 2 d. The laboratory tests showed elevated lipase and amylase levels. CT showed mild pancreatitis. There were no symptoms of COVID-19, which was confirmed by PCR. The patient was treated conservatively. He was discharged after 3 d in stable condition[41].

Kandasamy[42] reported the case of a 45-year-old woman with epigastric pain radiating to the back, nausea, and vomiting for 2 d, without cough, dyspnea, or fever. Laboratory tests showed elevated serum amylase and lipase levels and leukocytosis. Abdominal CT showed COVID-19 pneumonia as well as pancreatic and peripancreatic edema, inflammation, and collection, and acute interstitial edematous pancreatitis was diagnosed. CT severity index score was 4. The patient was discharged after conservative treatment[42].

Akarsu *et al*[43] prospectively assessed 367 patients treated between March 25, 2020 and April 25, 2020 for COVID-19 pneumonia. The authors investigated pancreatic injury caused by SARS-CoV-2 and the effects of AP on COVID-19 outcome. The diagnosis of AP was confirmed based on the revised Atlanta criteria. COVID-19 patients with confirmed AP were considered Group P ($n = 40$), and COVID-19 patients without AP were considered Group C ($n = 276$). AP was noted in 12.6% of the 316 patients. There were 50 (15.8%) patients with mild AP, 189 (59.8%) with severe AP, and 77 (24.3%) with critical disease. AP was not recorded among mild patients. AP was observed in 7.9% ($n = 15$) of patients with severe and 32.5% ($n = 25$) with critical status. A positive correlation between the severity of pneumonia and severity of AP was noted. The prevalence of AP increased with the severity of pneumonia ($P < 0.0001$). The duration of hospital stay was higher in Group P (14.7 ± 9.5 d) than in Group C (11.2 ± 6.4 d) ($P = 0.038$). Mortality was also higher in Group P (32.5% *vs* 7.97%, $P < 0.0001$). Moreover, the use of oxygen and mechanical ventilation was significantly greater in Group P ($P = 0.0006$ and $P = 0.0001$, respectively). Additionally, in patients with AP, the APACHE II score was higher (28.7 ± 6.8 *vs* 22.0 ± 2.7 , $P = 0.3685$). The authors concluded that AP alone could cause mortality and lead to altered immune response in the progression of COVID-19. Their results indicated that the presence of pancreatic injury triggered by SARS-CoV-2 deteriorated the patients' clinical conditions and increased mortality[43].

Tollard *et al*[44] reported the case of a 32-year-old female patient with obesity (BMI = 40.4 kg/m²), and dyspnea, polydipsia, and polyuria for several weeks. In the first-degree family history, insulin-dependent diabetes was noted. At admission, severe diabetic ketoacidosis (with hyperleukocytosis, normal liver function, and normal lipase levels) was observed. She was treated in the ICU and rehydration, intravenous insulin therapy, and intravenous potassium supplementation were used. On day 2, ketoacidosis disappeared, but fever (39.1 °C), dry cough, and epigastric pain appeared. Blood tests showed an inflammatory syndrome (increased procalcitonin), increased lipasemia, and altered liver functions associated with hepatocellular insufficiency. On CT, typical pulmonary signs of SARS-CoV-2 infection (lung involvement > 50%) and severe pancreatitis (diffuse pancreatic and peripancreatic edema and inflammation) were reported. The patient was intubated and ventilated. Circulatory support and broad-spectrum antibiotics were administered. Insulin therapy was continued. A rapid deterioration of clinical course (vasoplegic shock refractory to treatment, liver insuffi-

ciency, and disseminated intravascular coagulation) was noted. She died 7 d after her admission. The authors highlighted the influence of severe COVID-19 infection on pancreatic injury and alteration of glucose metabolism[44].

Alwaeli *et al*[45] reported the case of a 30-year-old man with fever, abdominal pain for 2 d, dry cough, nausea, vomiting, diarrhea for 4 d, and increasing dyspnea. The patient reported watery diarrhea for the previous 2 wk, a decrease in appetite, and abdominal pain 2 d prior. Hyperamylasemia and hyperlipasemia were shown in blood tests. CT showed COVID-19 pneumonia and pancreatic and peripancreatic edema and inflammation. ARDS with severe AP secondary to COVID-19 infection was diagnosed. The patient was admitted to the ICU, and conservative treatment (zero diet, intravenous fluids, total parenteral nutrition, antibiotics, antiemetics, and analgesics) was used. His clinical condition improved after 3 d of therapy. The patient was discharged from the hospital after clinical improvement[45].

Narang *et al*[46] reported the case of a 20-year-old pregnant woman hospitalized for sudden respiratory decompensation in the setting of confirmed COVID-19 infection with obesity (BMI = 36.1 kg/m²) and following cholecystectomy 2 years prior. CT showed COVID-19 pneumonia. Conservative treatment (remdesivir, dexamethasone, and betamethasone for fetal lung maturation) was used. On day 3, epigastric pain radiating to the back, nausea, and vomiting appeared. Laboratory studies showed elevated lipase and amylase levels. Abdominal magnetic resonance showed AP, without evidence of pancreatic hemorrhage, pseudocyst, or necrosis. On day 6, a preterm vaginal delivery developed. After delivery, her clinical condition improved. She was discharged in stable condition on postpartum day 3[46].

Miró *et al*[47] retrospectively analyzed all COVID patients diagnosed with AP in 62 Spanish EDs (20% of Spanish EDs, COVID-AP). Two control groups, namely, COVID-19 patients without AP (COVID-non-AP) and non-COVID-19 patients with AP (non-COVID-AP), were formed. Fifty-four cases of AP in 74814 patients with COVID-19 attending the ED were noted. This frequency was lower than that in non-COVID-19 patients (2231 in 1388879 patients). The etiology of AP (including biliary origin in approximately 50%) was comparable in the groups, and 26 clinical parameters of COVID-19 patients were associated with a higher risk of AP: Abdominal pain, vomiting, and raised blood amylase and inflammatory markers (C-reactive protein, procalcitonin, platelets, and D-dimer). There were 23 features differing COVID-AP from non-COVID-AP patients. Less frequent abdominal pain, lower pancreatic enzyme increases, and higher severity were noted in COVID-AP patients. The in-hospital mortality was comparable in COVID-AP and COVID-non-AP patients but it was higher than that of non-COVID-AP patients. The authors concluded that AP as a presenting form of COVID-19 was unusual (< 1% cases)[47].

Inamdar *et al*[9] published a retrospective observational cohort study of adults admitted to 12 hospitals within the Northwell Health System from March 1, 2020 to June 1, 2020 during the COVID-19 pandemic in New York. The patients were identified as presenting with AP on admission if they met all three of the following criteria: (1) Lipase level greater than 3 times the upper limit of normal; (2) Radiological imaging (CT or magnetic resonance imaging) demonstrating pancreatitis; and (3) Upper abdominal pain at admission. During the study period, 48012 patients were hospitalized, and 11883 (24.75%) of 48012 were COVID-19-positive on admission. A total of 189 (0.39%) of 48012 met the criteria for a diagnosis of AP, and 32 (17%) of 189 were COVID-19 positive (pancreatitis prevalence of 0.27% among patients hospitalized with COVID-19). SARS-CoV-2-negative and SARS-CoV-2-positive patients with AP were compared. The Charlson Comorbidity Index and Bedside Index of Severity in Acute Pancreatitis scores were similar in the two groups. There was a higher proportion of Black and Hispanic patients with AP in the COVID-19-positive group than in the COVID-19-negative group ($P = 0.03$). In COVID-19-negative patients, biliary and alcohol etiologies were most common (34% and 37%, respectively), similar to those of the general population. However, among patients with COVID-19, these etiologies accounted for only 16% and 6% of cases, respectively. Idiopathic pancreatitis was the most common etiology in this group (69%, compared to 21% in COVID-19 negative patients ($P < 0.0001$)). This “idiopathic” pancreatitis could indicate a viral etiology in COVID-19-positive patients. Moreover, hospital stay was significantly longer (21.22 ± 26.91 vs 6.36 ± 5.83 d, $P < 0.001$), and mechanical ventilation was more frequent (28.13 ± 9 vs 6.37 ± 10 d, $P < 0.0011$) in COVID-19-positive patients than in COVID-19-negative patients[9].

Gubatan *et al*[48] published a retrospective analysis of the incidence, risk factors, and outcomes of COVID-19 among patients with a history of pancreatitis who tested positive for SARS-CoV-2 between March 4 and April 14, 2020. Among the analyzed patients, 0.7% (102/14235) had a history of acute or chronic pancreatitis. Obesity,

smoking status, alcohol use, diabetes mellitus, and ACE inhibitor or angiotensin receptor blocker use among patients with or without COVID-19 were similar. In univariate analysis, Asian ethnicity (odds ratio [OR] = 6.45, $P = 0.023$), prior COVID-19 exposure (OR = 7.31, $P = 0.019$), prior idiopathic pancreatitis (OR = 11.28, $P = 0.026$), and hypertension (OR = 7.44, $P = 0.018$) were associated with a higher risk of COVID-19. In multivariate analysis, Asian ethnicity (OR = 8.87, $P = 0.042$), idiopathic pancreatitis (OR = 27.15, $P = 0.026$), and hypertension (OR = 17.19, $P = 0.008$) were independently associated with a higher risk of COVID-19. AP was not observed in any patients with a history of pancreatitis with COVID-19. The authors concluded that the prevalence of COVID-19 among patients with prior pancreatitis was 7.8%, and it was higher than the population-weighted prevalence of SARS-CoV-2-positive serology in the background population (2.8%). In the authors' opinion, this suggested that patients with a history of pancreatitis might be more susceptible to COVID-19, and COVID-19 might not lead to a higher risk of SARS-CoV-2-induced pancreatitis because AP was reported in none of their patients with prior pancreatitis[48].

Jespersen Nizamic *et al*[49] described a very interesting 49-year-old woman with chronic renal insufficiency secondary to focal segmental glomerulosclerosis. She underwent renal transplant and presented with abdominal pain, diarrhea, generalized weakness, and menorrhagia, with increased creatinine and lipase, anemia, and thrombocytopenia in laboratory tests. CT demonstrated peripancreatic edema and fluid. The patient was positive for SARS-CoV-2, but she did not demonstrate any respiratory symptoms. Only mild atelectasis, with no pneumonia, was demonstrated in chest radiographs. The authors reported the first case of biopsy-proven thrombotic microangiopathy in a COVID-19 renal transplant recipient with AP and microangiopathic hemolytic anemia. Therefore, AP in this case may have resulted from thrombotic microangiopathy[49].

Cheung *et al*[50] described the case of a 38-year-old man with fever and epigastric pain. Laboratory testing revealed a high lipase level. Abdominal CT showed AP. A diagnosis of idiopathic AP was made. He received conservative management with intravenous fluids, became medically stabilized, and was discharged[50].

Szatmary *et al*[51] described a cohort of five patients with AP and COVID-19 hospitalized at the Royal Liverpool University Hospital. All the five patients were young adult men (median age was 42 years) who were overweight or obese (median BMI was 30 kg/m²). Abdominal CT revealed mild pancreatic edema without significant pancreatic or peripancreatic necrosis, with distinct duodenal/periduodenal inflammation involving the second and third portions of the duodenum. Intravenous fluids were used in all patients. Three patients received insulin and/or fibrinolytic therapy, oral feeding, and analgesics. Four patients received broad-spectrum intravenous antibiotics due to associated pneumonia. Corticosteroid and organ support therapy were not needed. Thus, moderate AP based on the presence of acute fluid collections alone was recognized in all patients. Median length of stay was 14 (range, 6-16) d. In that study, transient dyslipidemia and impaired glucose tolerance were observed in patients, and in the authors' opinion, this observation needs further investigation[51].

We should add that according to some authors, the etiological association between AP and COVID-19 is controversial. Juhász *et al*[52] questioned the role of COVID-19 in AP etiology. In the authors' systematic review registered with PROSPERO as "Pancreas involvement in COVID-19: A systematic review", six case reports and two retrospective cohort studies were analyzed. In all AP cases, SARS-CoV-2 infection was confirmed by RT-PCR, but proper etiological analysis was absent. Despite the revised Atlanta criteria[53] used for AP recognition, a high risk of bias in case reports was noted by the authors. The authors strongly advised all clinicians to perform proper etiological analysis before a diagnosis of COVID-19-related AP. In the authors' opinion, the potential mechanisms of pancreatic injury in COVID-19 should be investigated by basic research studies using animal models in order to assess a possible etiological association between SARS-CoV-2 and AP[52].

SUMMARY OF THE LITERATURE REVIEW

Summary of case reports

AP may be associated with COVID-19 infection. Summary analysis of the reviewed case reports revealed that the mean age of patients was 46 (range, 20-68) years. There were 11 (55%) females and 9 (45%) males in all reviewed case reports. In most patients, the following symptoms were observed: Fever, dry cough, progressive dyspnea, and typical gastrointestinal symptoms such as epigastric pain, nausea, vomiting, and

diarrhea for 8 d. Epigastric pain was the most common symptom. The period between AP manifestation and COVID-19 onset varied, from 0 to 23 d between the first COVID-19 and AP symptoms (mean period was 7 d). In 11 cases, the manifestation of AP was reported several days (from 2 to 14 d) before COVID-19 presentation and confirmation. In all patients, COVID-19 infection was confirmed by RT-PCR. The mean age of patients was 46 (range, 20-68) years. Among 33 reported patients, there were 17 (51.5%) females and 16 (48.5%) males in all reviewed case reports. Mild AP was the most frequent [22 (66.7%)] AP severity degree. There were two (6.0%) cases of moderate severe pancreatitis and nine (27.3%) patients with severe AP. All patients were treated conservatively with bowel rest, intravenous crystalloid fluid resuscitation, prokinetics, and analgesic drugs. Additional nutritional support, including parenteral nutrition, antibiotics, and antiviral drugs, was used in some cases. No patients required surgery. Hospitalization in ICU was needed in 24 (72.7%). In all patients, hospitalization was associated with coexisting pneumonia and respiratory insufficiency. Most patients (28, 84.8%) recovered. Only three (9.1%) patients died, and in two (6.1%) patients, follow-up was not completed during case presentation. In most patients, prognosis was determined by coexisting COVID-19 pneumonia, which was noteworthy for almost all of them. Case reports are summarized in [Table 1](#).

Summary of cohort studies

The analysis of seven cohort studies (six retrospective and one prospective) showed a significantly higher incidence of “idiopathic” AP in COVID-19 patients than in non-COVID-19 patients[9,48]. In the Dirweesh *et al*[27]’s study, higher Charlson Comorbidity Index, mortality, and MOF were observed in COVID-19 (+) patients than in COVID-19 (-) patients, but age, sex, infected necrosis, venous thrombosis, and endocrine insufficiency rates were comparable in the two groups[27]. Miró *et al*[47] noted a higher mortality in COVID-19-positive patients than in non-COVID-19 patients with AP. These authors also reported a higher AP severity in COVID-19 patients[47]. Inamdar *et al*[9] found comparable Charlson Comorbidity Index, age, sex, pancreatic necrosis, and mortality in the two groups but longer hospitalization and mechanical ventilation prevalence in COVID-19-positive AP patients than in COVID-19-negative AP patients[9]. To sum up these findings, coexistence of AP with COVID-19 disease is associated with a worse prognosis than AP without SARS-CoV-2 infection. A summary of the most important findings of the cohort studies is presented in [Table 2](#).

Limitations of presented studies

In some case reports, confirmation of COVID-19 by laboratory PCR tests was made several days after AP manifestation or respiratory symptoms. Therefore, an exact conclusion regarding the period between AP and COVID-19 onset is not possible. In these patients, the numbers of days in the period between the PCR test and AP are presented in brackets in [Table 1](#). In some patients, the first AP symptoms appeared several days following treatment of AP. In our opinion, in these patients, another cause of AP (analgesics or antibiotics) cannot be ruled out. We agree with the opinion of Juhász *et al*[52] that there is a risk of bias in reviewed case reports, particularly in patients for whom AP appeared a longer time after treatment of COVID-19.

The limitations of cohort studies are associated with retrospective analysis and small numbers of patients in the analyzed cohorts. These limitations are associated with the novelty of this topic. Further prospective, multicenter studies including larger cohorts are needed.

CONCLUSION

COVID-19 is a multisystemic disease caused by SARS-CoV-2 with various clinical manifestations ranging from mild upper respiratory symptoms to ARDS. Numerous studies have demonstrated an association between COVID-19 and AP. AP in severe COVID-19 patients may be caused by direct attack of SARS-CoV-2 to pancreatic acinar cells or indirect, altered systemic inflammatory response from cytokine storm syndrome causing multiorgan dysfunction, including pancreatic injury or locoregional vasculitis and thrombotic microangiopathy secondary to COVID-19. In our opinion, symptoms from the onset of the disease indicate direct pancreatic damage by the virus. The evidence for direct pancreatic injury, as a result of viral amplification, is SARS-CoV-2 RNA detection in a pancreatic pseudocyst sample by Schepis *et al*[22]. Pancreatitis symptoms appearing after several days of disease duration may have resulted from a cytokine storm and generalized hyperinflammatory response.

The literature review shows that SARS-CoV-2 appears to be a new etiological infectious factor of AP. All reported cases were confirmed and documented using the revised Atlanta criteria[53] for AP recognition: (1) Abdominal pain; (2) Elevated amylase or lipase (> 3 times the upper limit); and (3) Results of radiological studies plus PCR test for confirmation of SARS-CoV-2 infection. COVID-19-associated AP occurs in each sex and at every age, in patients with and without comorbidities. AP in COVID-19 may be reported at the beginning or after several days of the disease. Usually, it is associated with pneumonia. Mild pancreatitis is the most common. The course of AP in COVID-19 patients is most frequently not severe. Prognosis is commonly determined by pneumonia in COVID-19 patients. Treatment of AP is typical and includes intravenous fluids, occasionally enteral or parenteral nutrition, analgesics, antibiotics, *etc.* Frequently, antiviral treatment is additionally used.

Therefore, there is strong evidence for an association between AP and COVID-19, but the diagnosis of COVID-19-related AP is challenging, because other potential etiological factors must be ruled out[33]. It is important to pay attention to the association between COVID-19 infection and AP[11]. All known etiological factors, including drugs used in COVID-19 disease, should be ruled out to recognize AP secondary to COVID-19. On the other hand, in some cases, AP may not be a consequence of SARS-CoV-2 infection but may coexist independently from COVID-19.

Answering the question in the title of this article, our knowledge on SARS-CoV-2, including knowledge about the exact relationship between AP and COVID-19 infection and the pathomechanism of AP secondary to SARS-CoV-2 infection, is limited and needs to be supplemented by further studies involving animal model experiments and multicenter cohort studies involving large numbers of patients. It is important to create appropriate therapeutic strategies for patients with AP and COVID-19.

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