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Surgical intervention for acute pancreatitis in the COVID-19 era

Su YJ and Chen TH. Surgical intervention for acute pancreatitis

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Abstract

Approximately 15%-19%⁴ of patients with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infections develop gastrointestinal symptoms.³⁰ Acute pancreatitis (AP) has been reported in 0.1%²⁷ of patients with coronavirus disease 2019 (COVID-19). Biliary AP was most common (78.4%)² before the COVID-19 pandemic; idiopathic AP is most common in patients with COVID-19 (up to 57.1%). The number of emergency department presentations decreased by 23.3% during the pandemic and many governments made⁷ national recommendations to delay nonurgent endoscopic procedures, leading to decrements of 22% in⁷ combined esophagogastroduodenoscopy (EGD) and colonoscopy and 20% in EGD after the⁴ COVID-19 pandemic. The symptoms and signs of COVID-19-related AP are fever (63%), abdominal pain (58%), respiratory symptoms (40%), nausea and vomiting (39%), and headache (4%). Approximately 5-10% of patients develop necrotizing or hemorrhagic AP, and patients who required surgical intervention had a higher mortality risk. Compared to 2019, the rates of elective surgery decreased by 41.8% in 2020; including cholecystectomy (40.1% decrease) and pancreas (111.1% decrease). Surgical volumes also decreased by 18.7% in 2020; device-assisted¹¹ laparoscopic and robot-assisted

procedures reduced by 45.4% and 61.9% during the COVID-19 Lockdown in 2020.

Key Words: 2019-nCoV; Complications; COVID-19; Pancreatitis; Surgery

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Core Tip: Approximately 5%-10% of cases of acute pancreatitis (AP) develop necrotizing or hemorrhagic pancreatitis and require surgical intervention. Idiopathic causes were the leading etiology (57.1%) of coronavirus disease 2019 (COVID-19)-related AP. In COVID-19-related pancreatitis, gastrointestinal symptoms developed 1.7 days later than respiratory symptoms (9.0 d vs 7.3 d). Regarding examination of the pancreatitis, there was a 57.5% reduction in endoscopic retrograde cholangiopancreatography in 2020 compared to 2019. Moreover, COVID-19-related AP is associated with a 2.7-fold admission rate, 3.4-fold mortality rate, and 3-fold intensive care unit admission rate than non-COVID-19-related AP.

INTRODUCTION

Acute pancreatitis (AP) is a common medical emergency observed in daily practice. The majority of patients with AP experience an uncomplicated course after palliative management. However, approximately 5%-10% of cases develop necrotizing or hemorrhagic pancreatitis, and patients with progressive organ failure, infectious complications, or who require surgical intervention have higher rates of morbidity and mortality^[1].

¹ Coronavirus disease 2019 (COVID-19) has been linked to the development of diabetes and metabolic dysregulation resulting from expression of viral entry proteins in the exocrine cells and ductal epithelium of the pancreas; specifically, ²² expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) can lead to pancreatic disorders^[2]. Thus, ¹ SARS-CoV-2 infections among patients with AP have raised concern among physicians and surgeons who treat this digestive system emergency.

Undoubtedly, people who were hesitant or reluctant to seek medical help during the COVID-19 pandemic may have delayed surgical evaluation and not undergone necessary resection^[3]. Due to fears related to viral transmission, the number of emergency department presentations in New Zealand decreased by 23.3% in year compared to 2019^[4]. The COVID-19 pandemic also led to ¹⁶ a reduction in the number of surgical resections and increased adoption of non-surgical management for pathologies that were traditionally treated surgically^[5]. On the other hand, many governments published ⁷ national recommendations to delay nonurgent endoscopic procedures, which lead to decrements of 49% in colonoscopy, 22% in ⁷ combined esophagogastroduodenoscopy (EGD) and colonoscopy, and 20% in EGD during the pandemic in United States^[6]. Thus, some examinations for pancreatic disorders were delayed and conservative waiting times for definitive surgery increased^[7]. This review focuses ⁴ on the features of AP in patients with COVID-19, the differences ²⁵ between COVID-19-related AP and non-COVID-19-related AP, and ⁴ the impact of the COVID-19 pandemic on the management of and surgical interventions for AP.

ETIOLOGIES OF NON-COVID-19 RELATED AND COVID-19-RELATED

AP

AP may result from bile duct or gallstone-related pancreatitis, a recent history of alcohol abuse or consumption, usage of some medications, hypertriglyceridemia, extracorporeal shock wave lithotripsy (ESWL), post-endoscopic retrograde cholangiopancreatography (ERCP), genetic causes, trauma that causes pancreatic duct injury, hypercalcemia, and infections; idiopathic factors have also been hypothesized to cause AP^[1,8,9]. COVID-19-AP has been associated with a significant increment (2.5-fold) in the incidence of idiopathic pancreatitis compared to patients without COVID-19. This observation suggests that the SARS-CoV-2 virus may cause AP^[10,11]. A study conducted in Serbia described that 15%-19% of patients with SARS-CoV-2 infections developed gastrointestinal symptoms^[12,13].

Generally speaking, before the COVID-19 pandemic, biliary pancreatitis was the most common etiology (78.4%) among patients admitted to hospital for AP, followed by idiopathic AP (16.8%)^[11]. AP was detected in 0.1% of patients with COVID-19. Gallstones were an etiologic factor in 28.6% of patients who developed AP during the COVID-19 pandemic, and hyperlipidemia was a factor in 14.3% of patients. However, an etiologic factor could not be determined in 57.1% of cases of COVID-19-related AP; these cases were regarded as having an idiopathic etiology^[11].

Research conducted in the US in April 2022 stated that evidence to establish a causal relationship between SARS-CoV-2 infection and AP was lacking^[14]. However, a UK study reported that SARS-CoV-2 infection increases the risk of idiopathic AP, but not long-term diabetes. Thus, further laboratory studies that prove the SARS-CoV-2 virus replicates in human pancreatic cells and

causes subsequent cell injury are warranted to establish SARS-CoV-2 as an etiology of AP^[10,15].

POTENTIAL MECHANISMS OF COVID-19-RELATED AP

Hyperlipidemia was commonly observed in patients with COVID-19, with an incidence of 33%. Hypertriglyceridemia has become one of the leading causes of AP in recent years. Thus, the current narrative review aimed to explore the associations between AP, COVID-19, and hyperlipidemia. Although the incidence of pancreatitis in the COVID-19 population was relatively low, substantial numbers of cases of COVID-19 complicated with AP were reported. Thus, hyperlipidemia could be a mediating factor in the pathogenesis of AP in patients with COVID-19^[16].

The location of the virus-host cell receptors angiotensin-converting enzyme 2 and transmembrane serine protease 2 plays an important role in the pathophysiology and presentation of COVID-19. These receptors are expressed in the respiratory tract, as well as other organs and tissues including exocrine and endocrine pancreatic cells^[12]. Additionally, systemic inflammation may cause AP, especially in children. The levels of immune mediators associated with AP-including interleukin (IL)-1 β , IL-10, interferon- γ , monocyte chemotactic protein 1, and tumor necrosis factor- α (TNF- α) are higher in the plasma of patients with COVID-19, which suggests the pancreas is indirectly involved in COVID-19^[17]. Moreover, some of the clinical features of AP complicate COVID-19, such as the high complication rate of pancreatic necrosis, severe AP, and high mortality^[17].

SYMPTOMS OF COVID-19-RELATED AP

The respiratory symptoms of SARS-CoV-2 are well-recognized; however, SARS-CoV-2-infected patients with AP also develop gastrointestinal symptoms. A study of 82 patients with COVID-19 who developed AP identified abdominal pain as the major symptom (91.5%); fever (59.8%), vomiting (58.5%), and nausea (47.6%) were also reported^[17]. Another study that investigated 42 patients revealed most patients suffered from typical epigastric pain (31%), followed by pain radiating to the back (29%), or diffuse abdominal pain (19%), though some patients did not report abdominal pain (7%)^[18]. While both respiratory and gastrointestinal symptoms could occur concomitantly, one study found that gastrointestinal symptoms occurred subsequently to the respiratory symptoms (9.0 d vs 7.3 d)^[19]. Another study revealed that 70% of patients with COVID-19-related AP complained of abdominal pain upon admission to the hospital, with 30% of these patients suffering abdominal pain during their entire period of hospitalization^[18]. Other studies assessing the symptoms of AP in patients with COVID-19 were limited by small sample sizes or the sedation status of the patients^[20,21]. Overall, further research and better documentation of the clinical symptoms of AP among patients with COVID-19 are needed.

Comparison of the symptoms of patients with AP with and without COVID-19 revealed major differences in the rates of fever (63%) and respiratory symptoms (40%) (Table 1). The typical symptoms of AP include fever, epigastric abdominal pain, nausea, vomiting, diarrhea, or shock^[8,22]. We found the majority of COVID-19 patients with AP suffered respiratory symptoms. However, this result should remind physicians to consider AP in patients with COVID-19, even if the patients do not complain of gastrointestinal symptoms^[17,20,23,24].

MANAGEMENT OF COVID-19-RELATED AP

General principles including nil ⁶ by mouth are always suggested to prevent the release of inflammatory mediators after ingestion for AP; in addition to ⁶ pain control and nutritional support, fluid supplementation is the main component of therapy^[8]. If necrotic gas-forming changes or hemorrhage occur, then curettage of the necrotic tissues is necessary. The surgical ⁶ treatment strategy includes early administration of antibiotics and percutaneous drainage of collected fluid, followed by ⁶ surgical resection of the infected necrotic tissue^[8]. ¹ Gas-forming bacteria may reach the pancreatic bed *via* the bloodstream, lymphatic channels, fistula of the nearby bowel, translocate from the transverse colon, or reflux *via* the opening of the ampulla of Vater^[1].

However, during the COVID-19 pandemic, many surgical interventions were postponed to prevent transmission of the virus, and surgery following intensive protective arrangements was recommended ⁴ during the COVID-19 pandemic^[25]. A UK study in 2021 reported ERCP was an important immediate examination and treatment for several kinds of biliary pathologies, including obstructing ductal stones and a range of malignancies. Compared to 2019, there was a 57.5% reduction in ERCP in 2020 ¹⁷ due to the impact of the COVID-19 pandemic^[26]. ⁷ The median time to endoscopy for AP after a delayed procedure due to COVID-19 was 88 d^[6].

SURGICAL INTERVENTIONS FOR COVID-19-RELATED AP

⁸ Treatment for AP was mostly supportive, with varied therapies employed for patients with COVID-19. More than half of these ⁸ cases were considered

idiopathic and presumed to be SARS-CoV-2-induced as established etiological factors were reported^[11]. AP should be considered in COVID-19, especially in patients exhibiting gastrointestinal symptoms.

In response to the pandemic, many surgeries were postponed or canceled due to COVID-19, especially surgery for the pancreas^[27]. Elective surgery decreased by 41.8% compared to 2019, including hernial surgery (63.9% decrement), cholecystectomy (40.1% decrement), liver surgery (16.7% decrement), and pancreatic surgery (111.1% decrement) in Singapore^[27]. A study from ten Italian referral centers ($n = 1423$) reported a 18.7% decrement in the surgical volume in 2020, with a 43.4% decrease in surgery for benign lesions and a decrease of 33.6% in operations for neuroendocrine tumors^[28]. The numbers of device-assisted surgeries, such as laparoscopic and robot-assisted procedures also dropped by 45.4% and 61.9% during the 2020 Lockdown due to the COVID-19 pandemic^[28].

COMPLICATIONS OF SURGICAL INTERVENTION FOR AP

Pancreatic leakage, hemorrhage, intra-abdominal abscesses, and delayed gastric emptying are possible postoperative complications of surgery for AP. Postoperative pancreatic fistula (POPF) is another complication after pancreatic surgery, and the relationship between sarcopenia and poorer outcomes raise concern^[29]. POPF develops in 17.2% of patients after laparoscopic pancreaticoduodenectomy; a soft texture of the pancreas is an independent risk factor for POPF. Bile fistula occurs in 6.4% of patients, and a history of cardiovascular disease, surgical time, pre-operative CA125, and pre-operative total bilirubin are independent risk factors for development of bile fistula^[30]. In terms of the method of surgical intervention, no significant

differences in the incidence of major complications, mortality, or rate of POPF were observed between the open method and minimally invasive method^[31]. Patients with COVID-19 who underwent pancreatic surgery had a 3.6-fold²¹ higher risk of perioperative mortality, 2.2-fold higher risk of major complications, 2.6-fold higher risk of late postoperative bleeding, and a 2.1-fold¹ higher risk of POPF^[32].

OUTCOME AND PROGNOSIS OF COVID-19-RELATED AP

³ Experimental and pathological evaluations suggest that SARS-CoV-2 infects human endocrine and exocrine pancreatic cells; thus, SARS-CoV-2 may be directly involved in pancreatic disorders^[17]. Hyperglycemia is frequently noted in patients infected with SARS-CoV-2, possibly as viral replication in¹⁴ beta cells may impair glucose-stimulated insulin secretion. Patients who recover from COVID-19 exhibit sustained glycemic abnormalities for 2 mo. Moreover, some patients developed diabetes mellitus during follow-up; both of these patients had severe necrotic AP, which is likely to be the cause of DM¹⁴ rather than SARS-CoV-2-induced damage^[10]. The association between the lipase/Lymphocyte ratio and predicting mortality was investigated in patients diagnosed with COVID-19 and AP^[33].

Research conducted in Italy and published in February 2022 pointed out that post-operative intensive care unit (ICU) admissions and postoperative mortality rates did not change significantly due to the indication for surgical intervention and resection for AP without delay during the pandemic COVID-19 era^[28]. No differences in the severity of AP (or acute appendicitis or acute diverticulitis) were detected in another study^[4]. However, given the fall in pancreatic transplantation activity and the increased risks associated

with COVID-19, waiting list mortality will inevitably increase^[34]. COVID-19-related AP has been related to the presence of edema or necrosis in radiological images, symptoms of abdominal pain in acute biliary pancreatitis, ²³ a longer length of hospital stay, ²³ and higher in-hospital mortality^[35-37]. A study in the United States reported a 2.7-fold higher admission rate, 3.4-fold increase in mortality, and 3-fold higher rate of intensive care unit admission for patients with COVID-19-related AP^[38]. Unfortunately, ¹⁰ there was also a small but worrying increase in patients with gallstone pancreatitis. Reduced cholecystectomy rates inevitably increase waiting lists and are likely, in time, to lead to an increase in the incidence of serious complications^[7]. ²⁸ Patients with COVID-19-related AP were found to have a mortality rate of 12.4%-18.5%^[37,38]; these values are higher than ¹ the overall mortality rate of 10.7% for emphysematous pancreatitis reported in a Asian study^[1]. ¹ Medical treatment had good outcomes in patients with stable emphysematous pancreatitis (35.7%); ¹ surgical necrosectomy was performed for the other 64.3% of patients with persistent decompensated organ failure^[1].

CONCLUSION

Around 15%-19% of patients with SARS-CoV-2 infections develop gastrointestinal symptoms and ¹⁹ approximately 5%-10% of patients develop necrotizing or hemorrhagic AP, which requires surgical intervention and has high rates of morbidity and mortality. Emergency department presentations reduced by 23.3% ¹⁷ due to the impact of the COVID-19 pandemic. Idiopathic causes were the leading etiology (57.1%) of COVID-19-related AP. While both respiratory and gastrointestinal symptoms can occur concomitantly, gastrointestinal symptoms typically develop 1.7 d later than respiratory

²⁶ symptoms (9.0 d *vs* 7.3 d). In terms of the clinical examination of AP, the COVID-19 pandemic led to a 57.5% reduction in ERCP and ⁷ the median time to endoscopy after a delayed procedure due to COVID-19 was 88 days. Elective surgery decreased by 41.8% compared to 2019, with a 40.1% decrement in cholecystectomy and 111.1% decrement in pancreatic surgery. Patients with COVID-19-related pancreatitis had a 2.7-fold higher admission rate, 3.4-fold higher mortality rate, and 3-fold higher intensive care unit admission rate than patients with AP who did not have COVID-19.

Table 1 Comparison of the symptoms of ² patients with acute pancreatitis with and without COVID-19

Ranking	Acute pancreatitis without ² COVID-19	Acute pancreatitis with COVID-19
1	Abdominal pain (94%)	Fever (63%)
2	Nausea & vomiting (88%)	Abdominal pain (58%)
3	Abdominal distension (40%)	Respiratory symptoms (40%)
4	Fever (12%)	Nausea & vomiting (39%)
5	Jaundice (10%)	Headache (4%)

COVID-19: Coronavirus disease 2019.

34%

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