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

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

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Contents

1. Introduction

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

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

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

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

2. Materials and methods

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

3. COVID-19 and the pancreas

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

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

With emergence of novel variants of COVID-19 and evidence obtained regarding the presentation of patients with COVID-19 infection, novel potential target organs have been identified based on expression of the angiotensin-converting enzyme 2 (ACE2) receptor that serves as the entry point into the cell for the virus (24). Xiao *et al* (21) found evidence of gastrointestinal infection with SARS-CoV-2 by detecting RNA and intracellular staining of the ACE2 receptor and viral nucleocapsid protein in gastric, duodenal and rectal epithelia. Studies using electron microscopy on tissue obtained from biopsies and/or autopsies have shown that the virus replicates highly in both small and large intestine (5,23-26). Patients with COVID-19 have viral RNA in their stools (27-31), which confirms the release of infectious virions in the gastrointestinal tract. For COVID-19 infection, fecal-oral transmission has been confirmed (32). In addition to being highly expressed in pericytes of the pancreatic microvasculature, ACE2 is expressed in human pancreatic cells and islets (5,33,34). Abnormal Laboratory results suggesting pancreatic injury have been detected in 8.0-17.5% of acute pancreatitis patients, with 7.0% showing substantial pancreatic alterations on computed tomography (35,36). It is currently unknown what causes pancreatic injury in patients with SARS-CoV-2. Pharmaceutical drugs consumed prior to hospitalization as well as pancreatic ACE2 expression may be involved (37). In COVID-19, patients may exhibit elevated amylase levels but not all of these patients have AP. Stephens *et al* (38) showed that although a significant population of critically ill patients with COVID-19 exhibit elevated serum amylase concentration, only 1.7% of patients had a confirmed diagnosis of AP and the serum amylase levels did not influence mortality. There may be several causes of elevated serum amylase levels, including generalized intestinal inflammation or impaired renal excretion (39). Elevated serum amylase in patients with COVID-19 is not frequently caused by AP or clinical damage to the pancreas but may be a non-specific manifestation of COVID-19 or sepsis.

4. AP in COVID 19-positive patients

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

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

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

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

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

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

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

5. AP during the COVID-19 pandemic

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

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

The pandemic led to a decrease in the general hospitalization rate of patients with various conditions due to fear. A decrease in the total number of hospitalizations of patients with AP was observed compared with before the pandemic (56,57). A potential reason is that instances with a moderately severe type of acute pancreatitis were discharged more rapidly (57), while patients with a mild form, as defined by the updated Atlanta classification (58), were no longer hospitalized. According to studies comparing hospitalizations for AP before the pandemic with hospitalizations during the pandemic, more severe forms of AP were present at the time of presentation in hospitals during the pandemic (56) and patients were more likely to develop systemic inflammatory response syndrome (40% vs. 25%) and pancreatic necrosis (14% vs. 10%) during this time (59).

6. COVID-19 vaccine and pancreatitis

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

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

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

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

7. Diagnostic and therapeutic approach

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

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

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

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

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

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

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

Because there is a wide variety of potential clinical courses due to involvement of different organs and tissue, it is key to define and stratify the severity of disease in patients with AP. Laboratory tests can be used to confirm the diagnosis of AP, however the limited predictive value of assessment methods makes them clinically irrelevant (70).

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

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

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

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

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

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

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

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

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

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

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

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

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

Limiting surgery to patients who are already critically ill may reduce the incidence of complications and death (114,115). Patients with COVID-19-related pulmonary symptoms and injuries underwent open surgical debridement, although only a limited percentage of them were candidates due to significant OF that made surgery impossible (67).

8. Conclusions

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

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

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Competing interests

The authors declare that they have no competing interests.

References

1. Wang F, Kream R and Stefano G: Long-Term respiratory and neurological sequelae of COVID-19. Med Sci Monit 26: e928996, 2020.
2. World Health Organization. COVID-19 Weekly Epidemiological Update [Online]. 2021. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19-20-april-2021 [Accessed on 4 March 2022].
3. National Center for Health Statistics. COVID-19 Death Data and Resources [Online]. 2021. Available from: https://www.cdc.gov/nchs/nvss/covid-19.htm [Accessed on 4 March 2022].
4. Matthay MA, Calfee CS, Zhuo H, Thompson BT, Wilson JG, Levitt JE, Rogers AJ, Gotts JE, Wiener-Kronish JP, Bajwa EK, *et al*: Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrom (START Study): A Randomised phase 2a safety trial. Lancet Respir Med 7: 154-162, 2019.
5. Akarsu C, Karabulut M, Aydin H, Sahbaz NA, Dural AC, Yegul D, Peker KD, Ferahman S, Bulut S, Dönmez T, *et al*: Association between Acute Pancreatitis and COVID-19: Could pancreatitis be the missing piece of the puzzle about increased mortality rates? J Invest Surg 35: 119-125, 2022.
6. Cholankeril G, Podboy A, Aivaliotis VI, Pham EA, Spencer SP, Kim D and Ahmed A: Association of digestive symptoms and hospitalization in patients with SARS-CoV-2 infection. Am J Gastroenterol 115: 1129-1132, 2020.
7. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, *et al*: China novel coronavirus investigating and research team a novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382: 727-733, 2020.
8. Hunt RH, East JE, Lanas A, Malfertheiner P, Satsangi J, Scarpignato C and Webb GJ: COVID-19 and gastrointestinal disease: Implications for the gastroenterologist. Dig Dis 39: 119-139, 2021.
9. Zippi M, Hong W, Traversa G, Maccioni F, De Biase D, Gallo C and Fiorino S: Involvement of the exocrine pancreas during COVID-19 infection and possible pathogenetic hypothesis: A concise review. Infez Med 28: 507-515, 2020.
10. Liu F, Long X, Zhang B, Zhang W, Chen X and Zhang Z: ACE2 Expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clin Gastroenterol Hepatol 18: 2128-2130.e2, 2020.
11. Al Armashi AR, Somoza-Cano FJ, Patell K, Al Zubaidi A and Ravakhah K: COVID-19, necrotizing pancreatitis, and abdominal compartment syndrome: A perfect cytokine storm? Cureus 13: e17230, 2021.
12. Yadav D and Lowenfels AB: The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 144: 1252-1261, 2013.
13. van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, Boermeester MA, van Goor H, Dejong CH, van Eijck CH, *et al*: A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 141: 1254-1263, 2011.
14. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG and Vege SS; Acute Pancreatitis Classification Working Group: Classification of acute pancreatitis-2012: Revision of the Atlanta classification and definitions by international consensus. Gut 62: 102-111, 2013.
15. Seppänen H and Puolakkainen P: Classification, severity assessment, and prevention of recurrences in acute pancreatitis. Scand J Surg 109: 53-58, 2020.
16. Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, Ball CG, Parry N, Sartelli M, Wolbrink D, *et al*: Executive summary: WSES Guidelines for the management of severe acute pancreatitis. J Trauma Acute Care Surg 88: 888-890, 2020.
17. Brisinda G, Vanella S, Crocco A, Mazzari A, Tomaiuolo P, Santullo F, Grossi U and Crucitti A: Severe acute pancreatitis: Advances and insights in assessment of severity and management. Eur J Gastroenterol Hepatol 23: 541-551, 2011.
18. https://pubmed.ncbi.nlm.nih.gov/?term=%28SARSCOV2+infection%29+AND+%28acute+pancreatitis%29&sort=date.
19. https://0q11o54cq-y-https-www-scopus-com.z.e-nformation.ro/results/results.uri?sort=plf-f&src=s&st1=SARS-COV2+infection&st2=acute+pancreatitis&sid=e66b8378b6130d4fe5ead15b407ac373&sot=b&sdt=b&sl=74&s=%28TITLE-ABS-KEY%28SARS-COV2+infection%29+AND+TITLE-ABS-KEY%28acute+pancreatitis%29%29&origin=searchbasic&editSaveSearch=&yearFrom=Before+1960&yearTo=Present&featureToggles=FEATURE_DOCUMENT_RESULT_MICRO_UI%3A1&sessionSearchId=e66b8378b6130d4fe5ead15b407ac373&limit=10.
20. Fagenholz PJ, Fernández-del Castillo C, Harris NS, Pelletier AJ and Camargo CA Jr: Direct medical costs of acute pancreatitis hospitalizations in the United States. Pancreas 35: 302-307, 2007.
21. Xiao F, Tang M, Zheng X, Liu Y, Li X and Shan H: Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 158: 1831-1833, 2020.
22. Anand ER, Major C and Pickering O: Acute pancreatitis in a COVID-19 patient. Br J Surg 107: e182, 2020.
23. Pandanaboyana S, Moir J, Leeds JS, Oppong K, Kanwar A, Marzouk A, Belgaumkar A, Gupta A, Siriwardena AK, Haque AR, *et al*: SARS-CoV-2 infection in acute pancreatitis increases disease severity and 30-day mortality: COVID PAN collaborative study. Gut 70: 1061-1069, 2021.
24. Bita A, Mogosanu GD, Bejenaru LE, Oancea CN, Bejenaru C, Croitoru O, Rau G, Neamtu J, Scorei ID, Scorei IR, *et al*: Simultaneous quantitation of boric acid and calcium fructoborate in dietary supplements by HPTLC-densitometry. Anal Sci 33: 743-746, 2017.
25. Hanley B, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, Thursz M, Manousou P, Corbett R, Goldin R, *et al*: Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: A post-mortem study. Lancet Microbe 1: e245-e253, 2020.
26. Chmielik E, Jazowiecka-Rakus J, Dyduch G, Nasierowska-Guttmejer A, Michalowski L, Sochanik A and Ulatowska-Bialas M: COVID-19 autopsies: A case series from poland. Pathobiology 88: 78-87, 2021.
27. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, *et al*: Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382: 1708-1720, 2020.
28. Henry BM, de Oliveira MHS, Benoit J and Lippi G: Gastrointestinal symptoms associated with severity of coronavirus dis-ease 2019 (COVID-19): A pooled analysis. Intern Emerg Med 15: 857-859, 2020.
29. Du M, Cai G, Chen F, Christiani DC, Zhang Z and Wang M: Multiomics evaluation of gastrointestinal and other clinical characteristics of COVID-19. Gastroenterology 158: 2298-2301. e7, 2020.
30. Correia de Sá T, Soares C and Rocha M: Acute pancreatitis and COVID-19: A literature review. World J Gastrointest Surg 13: 574-584, 2021.
31. Rubin R: SARS-CoV-2 RNA can persist in stool months after respiratory tract clears virus. JAMA 327: 2175-2176, 2022.
32. Gu J, Han B and Wang J: COVID-19: Gastrointestinal manifestations and potential Fecal-Oral transmission. Gastroenterology 158: 1518-1519, 2020.
33. Dalan R, Bornstein SR, El-Armouche A, Rodionov RN, Markov A, Wielockx B, Beuschlein F and Boehm BO: The ACE-2 in COVID-19: Foe or Friend? Horm Metab Res 52: 257-263, 2020.
34. Shaharuddin SH, Wang V, Santos RS, Gross A, Wang Y, Jawanda H, Zhang Y, Hasan W, Garcia G Jr, Arumugaswami V and Sareen D: Deleterious Effects of SARS-CoV-2 Infection on human pancreatic cells. Front Cell Infect Microbiol 11: 678482, 2021.
35. Zhou Z, Zhao N, Shu Y, Han S, Chen B and Shu X: Effect of gastrointestinal symptoms in patients with COVID-19. Gastroenterology 158: 2294-2297, 2020.
36. Aloysius MM, Thatti A, Gupta A, Sharma N, Bansal P and Goyal H: COVID-19 presenting as acute pancreatitis. Pancreatology 20: 1026-1027, 2020.
37. Annunziata A, Coppola A, Andreozzi P, Lanza M, Simioli F, Carannante N, Di Somma C, Di Micco P and Fiorentino G: Acute pancreatitis and COVID-19: A Single-center experience. J Multidiscip Healthc 14: 2857-2861, 2021.
38. Stephens JR, Wong JLC, Broomhead R, Stümpfle R, Waheed U, Patel P, Brett SJ and Soni S: Raised serum amylase in patients with COVID-19 may not be associated with pancreatitis. Br J Surg 108: e152-e153, 2021.
39. Abramczyk U, Nowaczyński M, Słomczyński A, Wojnicz P, Zatyka P and Kuzan A: Consequences of COVID-19 for the pancreas. Int J Mol Sci 23: 864, 2022.
40. Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, *et al*: Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: A systematic review and me-ta-analysis. Lancet Gastroenterol Hepatol 5: 667-678, 2020.

41. Miró Ò, Llorens P, Jiménez S, Piñera P, Burillo-Putze G, Martín A, Martín-Sánchez FJ and González Del Castillo J; Spanish Investigators in Emergency Situations TeAm (SIESTA) network: Frequency of five unusual presentations in patients with COVID-19: Results of the UMC-19-S1. Epidemiol Infect 148: e189, 2020.
42. Inamdar S, Benias PC, Liu Y, Sejpal DV, Satapathy SK and Trindade AJ; Northwell COVID-19 Research Consortium: Prevalence, Risk Factors, and Outcomes of Hospitalized Patients With Coronavirus Disease 2019 Presenting as Acute Pancreatitis. Gastroenterology 159: 2226-2228.e2, 2020.
43. Wang K, Luo J, Tan F, Liu J, Ni Z, Liu D, Tian P and Li W: Acute pancreatitis as the initial manifestation in 2 cases of COVID-19 in Wuhan, China. Open Forum Infect Dis 7: ofaa324, 2020.
44. Khadka S, Williams K and Solanki S: Remdesivir-associated pancreatitis. Am J Ther 29: e444-e446, 2022.
45. Allam MM, El-Zawawy HT, Ahmed SM and Abdelhamid MA: COVID-19 treatment: A potential cause of acute pancreatitis. Clin Case Rep 10: e6465, 2022.
46. Dirweesh A, Li Y, Trikudanathan G, Mallery JS, Freeman ML and Amateau SK: Clinical outcomes of acute pancre-atitis in patients with coronavirus Disease 2019. Gastroenterology 159: 1972-1974, 2020.
47. Wang F, Wang H, Fan J, Zhang Y, Wang H and Zhao Q: Pancreatic injury patterns in patients with Coronavirus Disease 19 pneumonia. Gastroenterology 159: 367-370, 2020.
48. Akkus C; Yilmaz H, Mizrak S, Adibelli Z, Akdas O and Duran C: Development of pancreatic injuries in the course of COVID-19. Acta Gastroenterol Belg 83: 585-592, 2020.
49. Karaali R and Topal F: Evaluating the effect of SARS-CoV-2 infection on prognosis and mortality in patients with acute pancreatitis. Am. J Emerg Med 49: 378-384, 2021.
50. Kumar V, Barkoudah E, Souza DAT, Jin DX and McNabb-Baltar J: Clinical course and outcome among patients with acute pancre-atitis and COVID-19. Eur J Gastroenterol Hepatol 33: 695-700, 2021.
51. Samanta J, Gupta R, Singh MP, Patnaik I, Kumar A and Kochhar R: Coronavirus disease 2019 and the pancreas. Pancreatology 20: 1567-1575, 2020.
52. Rosenbaum L: The untold toll-the Pandemic's effects on patients without covid-19. N Engl J Med 382: 2368-2371, 2020.
53. Rodriguez-Leor O, Cid-Álvarez B, Ojeda S, Martín-Moreiras J, Rumoroso JR, López-Palop R, Serrador A, Cequier A, Romaguera R, Cruz I, *et al*: Impact of the COVID-19 pandemic interventional cardiology activity in Spain. REC Interv Cardiol 2: 82-89, 2020.
54. Hartnett KP, Kite-Powell A, DeVies J, Coletta MA, Boehmer TK, Adjemian J and Gundlapalli AV; National Syndromic Surveillance Program Community of Practice: Impact of the COVID-19 pandemic on emergency department visits-USA, January 1, 2019-May 30, 2020. MMWR Morb Mortal Wkly Rep 69: 699-704, 2020.
55. Guo Q, Li A, Xia Q, Liu X, Tian B, Mai G, Huang Z, Chen G, Tang W, Jin X, *et al*: The role of organ failure and infection in necrotizing pancreatitis: A prospective study. Ann Surg 259: 1201-1207, 2014.
56. Radulescu PM, Davitoiu DV, Baleanu VD, Padureanu V, Ramboiu DS, Surlin MV, Bratiloveanu TC, Georgescu EF, Streba CT, Mercut R, *et al*: Has COVID-19 Modified the Weight of Known Sys-temic inflammation indexes and the New Ones (MCVL and IIC) in the assessment as predictive factors of complications and mortality in acute pancreatitis? Diagnostics (Basel) 12: 3118, 2022.
57. Samanta J, Mahapatra SJ, Kumar N, Elhence A, Dhar J, Gupta A, Dhooria A, Bhalla A, Prasad M, Das A, *et al*: Virus related acute pancreatitis and virus superinfection in the 'Dual disease' model of acute pancreatitis and SARS-Co-V2 infection: A multicentre prospective study. Pancreatology 22: 339-347, 2022.
58. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG and Vege SS; Acute Pancreatitis Classification Working Group: Classification of acute pancre-atitis-2012: Revision of the Atlanta classification and definitions by international consensus. Gut 62: 102-111, 2013.
59. Ramsey ML, Patel A, Sobotka LA, Lim W, Kirkpatrick RB, Han S, Hart PA, Krishna SG, Lara LF, Lee PJ, *et al*: Hospital trends of acute pancreatitis during the coronavirus disease 2019 pandemic. Pancreas 51: 422-426, 2022.
60. Pădureanu V, Boldeanu MV, Streaţă I, Cucu MG, Siloşi I, Boldeanu L, Bogdan M, Enescu AŞ, Forţofoiu M, Enescu A, *et al*: De-termination of VEGFR-2 (KDR) 604A>G polymorphism in pancreatic disorders. Int J Mol Sci 18: 439, 2017.
61. Ozaka S, Kodera T, Ariki S, Kobayashi T and Murakami K: Acute pancreatitis soon after COVID-19 vaccination: A case re-port. Medicine (Baltimore) 101: e28471, 2022.
62. Walter T, Connor S and Stedman C and Doogue M: A case of acute necrotising pancreatitis following the second dose of Pfizer-BioNTech COVID-19 mRNA vaccine. Br J Clin Pharmacol 88: 1385-1386, 2022.
63. Meo SA, Bukhari IA, Akram J, Meo AS and Klonoff DC: COVID-19 vaccines: Comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. Eur Rev Med Pharmacol Sci 25: 1663-1669, 2021.
64. Rosenblum HG, Hadler SC, Moulia D, Shimabukuro TT, Su JR, Tepper NK, Ess KC, Woo EJ, Mba-Jonas A, Alimchandani M, *et al*: Use of COVID-19 vaccines after reports of adverse events among adult recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advi-sory committee on immuniza-tion Practices-United States, July 2021. MMWR Morb Mortal Wkly Rep 70: 1094-1099, 2021.
65. Parkash O, Sharko A, Farooqi A, Ying GW and Sura P: Acute pancreatitis: A possible side effect of COVID-19 vaccine. Cu-reus 13: e14741, 2021.
66. Pfizer: Pfizer-BioNTech COVID-19 vaccine (BNT162, PF-07302048). Vaccines and related biological products advi-sory committee. [cited 13 April 2022].
67. COVID-19 mRNA Pfizer-BioNTech vaccine analysis print. All UK spontaneous reports received between 9 December 2020 and 30 June 2021 for mRNA Pfizer/BioNTech vaccine analysis print. 2021. [cited 13 April 2022]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1009453/COVID 19_mRNA_PfizerBioNTech_Vaccine_Analysis_Print_DPL_28.07.2021.
68. World Health Organization. VigiAccess. [cited 13 April 2022]. Available from: http://www.vigiaccess.org.
69. Boskabadi SJ, Ala S, Heydari F, Ebrahimi M and Jamnani AN: Acute pancreatitis following COVID-19 vaccine: A case report and brief literature review. Heliyon 9: e12914, 2023.
70. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, van Santvoort HC and Besselink MG: Acute pancreatitis. Lancet 396: 726-734, 2020.
71. Bulthuis MC, Boxhoorn L, Beudel M, Elbers PWG, Kop MPM, van Wanrooij RLJ, Besselink MG and Voermans RP: Acute pancreatitis in COVID-19 patients: True risk? Scand J Gastroenterol 56: 585-587, 2021.
72. Ding P, Song B, Liu X, Fang X, Cai H, Zhang D and Zheng X: Elevated pancreatic enzymes in ICU patients With COVID-19 in Wuhan, China: A retrospective study. Front Med (Lausanne) 8: 663646, 2021.
73. Yao J and Lv G: Association between red cell distribution width and acute pancreatitis: A cross-sectional study. BMJ Open 4: e004721, 2014.
74. Jeon TJ and Park JY: Clinical significance of the neutro-phil-lymphocyte ratio as an early predictive marker foradverse outcomes in patients with acute pancreatitis. World J Gastroenterol 23: 3883-3889, 2017.
75. Takada K, Takamori S, Yoneshima Y, Tanaka K, Okamoto I, Shimokawa M, Oba T, Osoegawa A, Tagawa T, Takenoyama M, *et al*: Serum markers associated with treat-ment response and survival in non-small cell lung cancer patients treated with anti-PD-1 therapy. Lung Cancer 145: 18-26, 2020.
76. Huang Y, Liu A, Liang L, Jiang J, Luo H, Deng W, Lin G, Wu M, Li T and Jiang Y: Diagnostic value of blood parameters for community-acquired pneumonia. Int Immunopharmacol 64: 10-15, 2018.
77. Chan JC, Chan DL, Diakos CI, Engel A, Pavlakis N, Gill A and Clarke SJ: The Lymphocyte-to-Monocyte ratio is a supe-rior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann Surg 265: 539-546, 2017.
78. Tan D, Fu Y, Tong W and Li F: Prognostic significance of lympho-cyte to monocyte ratio in colorectal cancer: A meta-analysis. Int J Surg 55: 128-138, 2018.
79. Li M, Deng Q, Zhang L, He S, Rong J and Zheng F: The pretreat-ment lymphocyte to monocyte ratio predicts clinical outcome for patients with urological cancers: A meta-analysis. Pathol Res Pract 215: 5-11, 2019.

80. Huang HL, Nie X, Cai B, Tang JT, He Y, Miao Q, Song HL, Luo TX, Gao BX, Wang LL and Li GX: Procalcitonin levelspredict acute kidney injury and prognosis in acute pancreatitis: A prospective study. PLoS One 8: e82250, 2013.
81. Banks PA and Freeman ML; Practice Parameters Committee of the American College of Gastroenterology: Practice guidelines in acute pancreatitis. Am J Gastroenterol 101: 2379-2400, 2006.
82. Tenner S, Baillie J, DeWitt J and Vege SS; American College of Gastroenterology: American College of Gastroenterology guideline: Management of acute pancreatitis. Am J Gastroenterol 108: 1400-1415, 2013.
83. Sarr MG: Early fluid 'resuscitation/therapy' in acute pancreatitis: Which fluid? Ann Surg 257: 189-190, 2013.
84. Pădureanu V, Florescu DN, Pădureanu R, Ghenea AE, Gheonea DI and Oancea CN: Role of antioxidants and oxidative stress in the evolution of acute pancreatitis (Review). Exp Ther Med 23: 197, 2022.
85. Bortolotti P, Saulnier F, Colling D, Redheuil A and Preau S: New tools for optimizing fluid resuscitation in acute pancreatitis. World J Gastroenterol 20: 16113-16122, 2014.
86. Çolak E and Çiftci AB: Acute biliary pancreatitis management during the coronavirus disease 2019 pandemic. Healthcare (Basel) 10: 1284, 2022.
87. Arvanitakis M, Ockenga J, Bezmarevic M, Gianotti L, Krznarić Ž, Lobo DN, Löser C, Madl C, Meier R, Phillips M, *et al*: ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. Clin Nutr 39: 612-631, 2020.
88. Dang SC, Wang H, Zhang JX, Cui L, Jiang DL, Chen RF, Qu JG, Shen XQ, Chen M and Gu M: Are gastric mucosal macrophages responsible for gastric injury in acute pancreatitis? World J Gastroenterol 21: 2651, 2015.
89. Darnell ME, Subbarao K, Feinstone SM and Taylor DR: Inactivation of the coronavirus that induces severe acute respiratory syndrome, SARS-CoV. J Virol Methods 121: 85-91, 2004.
90. Zhou L, Niu Z, Jiang X, Zhang Z, Zheng Y, Wang Z, Zhu Y, Gao L, Huang H, Wang X and Sun Q: SARS-CoV-2 targets by the pscRNA profiling of ACE2, TMPRSS2 and furin proteases. iScience 23: 101744, 2020.
91. Kerwat K, Graf J and Wulf H: Nosocomial infections. Anasthesiol Intensivmed Notfallmed Schmerzther 45: 30-31, 2010 (In German).
92. Michaelis M, Kleinschmidt MC, Bojkova D, Rabenau HF, Wass MN and Cinatl J Jr: Omeprazole increases the efficacy of acyclovir against herpes simplex virus type 1 and 2. Front Microbiol 10: 2790, 2019.
93. Taştemur Ş and Ataseven H: Is it possible to use proton pump inhibitors in COVID-19 treatment and prophylaxis? Med Hypotheses 143: 110018, 2020.
94. Bojkova D, McGreig JE, McLaughlin KM, Masterson GS, Widera M, Krähling V, Ciesek S, Wass MN, Michaelis M and Cinatl J jr: SARS-CoV-2 and SARS-CoV differ in their cell tropism and drug sensitivity profiles. bioRxiv: April 5, 2020 doi: 10.1101/2020.04.03.024257.
95. Murata A, Ohtani M, Muramatsu K and Matsuda S: Effects of proton pump inhibitor on outcomes of patients with severe acute pancreatitis based on a national administrative database. Pancreatology 15: 491-496, 2015.
96. Ma X, Liu L, Tong H, Tang S, Ye C, Tai Y and Tang C: A randomized controlled trial of proton pump inhibitors inthe treatment of acute pancreatitis patients: The benefits and harms. Gastroenterology 152 (Suppl): S73, 2017.
97. Contou D, Claudinon A, Pajot O, Micaëlo M, Longuet Flandre P, Dubert M, Cally R, Logre E, Fraissé M, Mentec H and Plantefève G: Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care 10: 119, 2020.
98. He S, Liu W, Jiang M, Huang P, Xiang Z, Deng D, Chen P and Xie L: Clinical characteristics of COVID-19 patients with clinically diagnosed bacterial co-infection: a multi-center study. PLoS One 16: e0249668, 2021.
99. Ginsburg AS and Klugman KP: COVID-19 pneumonia and the appropriate use of antibiotics. Lancet Glob Health 8: e1453-e1454, 2020.
100. Isenmann R, Runzi M, Kron M, Kahl S, Kraus D, Jung N, Maier L, Malfertheiner P, Goebell H and Beger HG; German Antibiotics in Severe Acute Pancreatitis Study Group: Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: A placebo-controlled, double blind trial. Gastroenterology 126: 997-1004, 2004.
101. Jiang K, Huang W, Yang XN and Xia Q: Present and future of prophylactic antibiotics for severe acute pancreatitis. World J Gastroenterol 18: 279-284, 2012.
102. Sakorafas GH, Lappas C, Mastoraki A, Delis SG and Safioleas M: Current trends in the management of infected necrotizing pancreatitis. Infect Disord Drug Targets 10: 9-14, 2010.
103. Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, Ball CG, Parry N, Sartelli M, Wolbrink D, *et al*: 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg 14: 27, 2019.
104. Stigliano S, Sternby H, de Madaria E, Capurso G and Petrov MS: Early management of acute pancreatitis: A review of the best evidence. Dig Liver Dis 49: 585-594, 2017.
105. De Waele JJ: Rational use of antimicrobials in patients with severe acute pancreatitis. Semin Respir Crit Care Med 32: 174-180, 2011.
106. Mourad MM, Evans R, Kalidindi V, Navaratnam R, Dvorkin L and Bramhall SR: Prophylactic antibiotics in acute pancreatitis: Endless debate. Ann R Coll Surg Engl 99: 107-112, 2017.
107. Diaz JJ Jr, Cullinane DC, Khwaja KA, Tyson GH, Ott M, Jerome R, Kerwin AJ, Collier BR, Pappas PA, Sangosanya AT, *et al*: Eastern association for the surgery of trauma. J Trauma Acute Care Surg 75: 376-386, 2013.
108. Gurusamy KS, Belgaumkar AP, Haswell A, Pereira SP and Davidson BR: Interventions for necrotising pancreatitis. Cochrane upper GI and pancreatic diseases group. Cochrane Database Syst Rev 137: 201-253, 2016.
109. Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, van Eijck CH, Fockens P, Hazebroek EJ, Nijmeijer RM, *et al*: Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: A randomized trial. JAMA 307: 1053-1061, 2012.
110. van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Bouwense SA, Bruno MJ, *et al*: Endoscopic or surgical step-up approach for infected necrotising pancreatitis: A multicentre randomised trial. Lancet 391: 51-58, 2018.
111. Mowery NT, Bruns BR, MacNew HG, Agarwal S, Enniss TM, Khan M, Guo WA, Cannon JW, Lissauer ME, Duane TM, *et al*: Surgical management of pancreatic necrosis. J Trauma Acute Care Surg 83: 316-327, 2017.
112. Haines K, Parker V, Ohnuma T, Krishnamoorthy V, Raghunathan K, Sulo S, Kerr KW, Besecker BY, Cassady BA and Wischmeyer PE: Role of early enteral nutrition in mechanically ventilated COVID-19 patients. Crit Care Explor 4: e0683, 2022.
113. Compher C, Bingham AL, McCall M, Patel J, Rice TW, Braunschweig C and McKeever L: Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and Enteral Nutrition. JPEN J Parenter Enteral Nutr 46: 12-41, 2022.
114. Besselink MG, van Santvoort HC, Nieuwenhuijs VB, Boermeester MA, Bollen TL, Buskens E, Dejong CH, van Eijck CH, van Goor H, Hofker SS, *et al*: Minimally invasive 'step-up approach' vs maximal necrosectomy in patients with acute necrotising pancreatitis (PANTER trial): Design and rationale of a randomised controlled multicenter trial [ISRCTN13975868]. BMC Surg 6: 6, 2006.
115. Hollemans RA, Bakker OJ, Boermeester MA, Bollen TL, Bosscha K, Bruno MJ, Buskens E, Dejong CH, van Duijvendijk P, van Eijck CH, *et al*: Superiority of step-up approach vs open necrosectomy in long-term follow-up of patients with necrotizing pancreatitis. Gastroenterology 156: 1016-1026, 2019.