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Review Article

Coronavirus disease 2019 and the pancreas

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has led to a world-wide pandemic since its onset in December of 2019. Although, a primary respiratory pathogen, over the ensuing period, its extra-pulmonary effects have come to the forefront. The virus, having multi-organ tropism, has been shown to affect a host of other organs beyond the lung, including the pancreas. The data on pancreatic involvement by COVID-19, however, have been limited. Moreover, whether the effects on the pancreas are due to the direct effects of the virus or is just an epiphenomenon is debatable. The prevalence of pancreatic injury and degree of injury are the other issues that need to be addressed. Pancreatic cancer has a dismal prognosis and the management of the same in the COVID era needs to be tailored assessing the risk-benefit ratio for the same. Additionally, pancreatic surgery increases not only the morbidity of the patient, but also the risk of the operator and burden on the health care system. Hence, the decision for such major procedures needs to be rationalized for optimum benefit during this pandemic. Similarly, for the endoscopist, pancreatic endoscopy needs to be carefully regulated to reduce risk to both the patient and the physician and yet deliver optimum patient care. This review gives a concise summary of various aspects of pancreatic involvement and pancreatic disease management during this pandemic.
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Introduction

The world has been shaken by the worst pandemic since the Spanish flu of 1918, by a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Since its first detection in Wuhan City of China in December 2019, it has ripped through more than 200 countries affecting more than 26 million people and claiming more than 800,000 lives as on 6th September, 2020 [1]. A part of the coronavirus family, coronavirus disease 2019 (COVID-19) is primarily associated with features of pneumonia, respiratory failure and death. However, with passage of time, increasing reports of its multi-system involvement have come forth. COVID-19 has been reported to involve the gastrointestinal (GI) tract, liver, pancreas, cardiovascular system, nervous system, ocular system and so on [2,3]. Since the report of the first case of COVID-19 having gastrointestinal (GI) complaints [4], additional reports have explored extra-pulmonary effects of the virus. Involvement of the pancreas secondary to viral infections is not uncommon. Commonly reported viruses affecting the pancreas include hepatotropic viruses such as hepatitis A, B, E, Epstein Barr virus, coxsackie virus, cytomegalovirus, herpes zoster virus, HIV, and viruses ceasing mumps, measles, and varicella-zoster. The mechanism of a viral infection causing pancreatic injury depends on the type of virus [5]. SARS-CoV-2 has also been found to affect the pancreas to varying degrees.

We here give a concise review of the relevant published articles and have summarized the overall incidence rates for pancreatic involvement in COVID-19. Moreover, strategies to be adopted for the management of patients with pancreatic cancer and those requiring pancreatic surgery have been outlined. The effect of COVID-19 infection on pancreas transplant recipients have also been reviewed. Finally, the recent guidance on the pancreatic endo-therapy has been briefed for the practicing gastroenterologists and pancreatologists.

Information sources and literature search

A literature review was carried out through PubMed, Medline and Google Scholar search engines for all relevant English-language articles/abstracts using a search query constructed with the

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following medical subject heading (MeSH) terms: ("severe acute respiratory syndrome coronavirus 2" OR "COVID-19" OR "coronavirus 2019" OR "SARS-CoV-2") AND ("pancreas" OR "pancreatitis" OR "hyperamylasaemia" OR "pancreatic cancer" OR " pancreatic surgery" OR "pancreatic transplant"). The reference list of the papers, webpages of major gastroenterology and hepatology journals and websites of World Health Organisation (WHO), and Centre for Disease Control (CDC) publications were reviewed and all relevant data extracted. Additional published and unpublished studies from other platforms such as medRxiv and Social Science Research Network (SSRN) were also searched. For the recommendations, all the latest guidelines of the major gastrointestinal and endoscopy societies were reviewed (including online suggestions and preproofs) by the authors and were framed into a narrative review.

SARS-CoV-2: The pathogen

Corona viruses are a family of viruses that is responsible for a significant fraction of the human common cold. They are enveloped, positive, single stranded RNA viruses that belong to the family *Coronaviridae* and the order *Nidovirales* [6]. The most frequently encountered ones causing mild upper respiratory infections are 229E, NL63, OC43 and HKU1. However, the ones which are zoonotic in origin, can infect humans and lead to more fatal disease [7], among which are Severe Acute Respiratory Syndrome-related Coronavirus (SARS-CoV), Middle East Respiratory Syndrome-related Coronavirus (MERS-CoV) and the recently detected novel coronavirus 2019 (SARS-CoV-2). The genome sequence of SAR-CoV-2 is about 89% identical to bat SARS-like-CoVZXC21 and 82% identical to human SARS-CoV [8]. The world has already witnessed pandemics of the former 2 strains, SARS (2002–2003) and MERS (2012). The third coronavirus was designated as SARS-CoV-2 by the International Committee on Taxonomy of Viruses and later rechristened as COVID-19 by WHO [9].

Electron micrograph images reveal its diameter to be 60–140 nm and appearance of a solar corona (crown like) due to the presence of spikes (diameter of 9–12 nm). A spike glycoprotein (S Glycoprotein) attaches the virus to the host cell membrane and is a key factor for host range restriction [10]. The virus been identified to have three subtypes: "A", "B". and "C" [11]. While "A" and "C" subtypes have been reported from USA and Europe, type "B" is found predominantly in East Asia.

Pathophysiology of pancreatic injury

Hypothesized to have originated from bats or through pangolins [12], COVID-19 uses angiotensin converting enzyme 2 (ACE 2) as a receptor akin to SARS-CoV. Pathogenesis for lung injury encompasses attachment of the virus to ACE2 receptor on the lung type 2 alveolar cells. Once the spike protein (S) attaches to the alveolar cells, it leads to a cytokine storm which results in alveolar flooding and denudation of the lining epithelium, hampering oxygen exchange and manifesting clinically as ARDS [13]. This ACE 2 receptor expression is not only present in the lungs, but is also in abundance in the esophageal epithelial cells, absorptive enterocytes of the ileum and colon, cardiovascular and renal tissues, and the pancreas [14]. In fact, messenger RNA levels of ACE2 were found to be higher in pancreas than the lung [15]. This explains the multi-organ tropism of the virus.

ACE 2 expression is noted both in the exocrine pancreatic glands as well as in the islets. The spike protein (S) engages ACE 2 as the entry receptor [16]. Additionally, the cell entry is facilitated by priming of the S protein by transmembrane protease serine 2 (TMPRSS2) or other proteases [17] (Fig. 1). Combined expression of both ACE 2 and TMPRSS2 is needed for the successful virus entry into the cell. In fact, single-cell RNA-sequencing studies have demonstrated that this co-expression is noted not only in the lung alveolar epithelial type 2 cells, but also in various organs including the pancreatic ß cells [18]. Moreover, the receptor affinity of SARS-CoV-2 to ACE2 is greater compared to SARS-CoV, which can explain the higher efficiency and enhanced transmissibility of SARS-CoV-2 [19]. Binding of the virus to ACE 2 receptor mediates pancreatic injury. Dysregulated immune response and cytokine burst have been seen in severe COVID-19 infection with higher levels of interleukin-6 (IL-6) found to be associated with worse prognosis [20,21]. Moreover, it has been noted that pancreatic injury was higher in severe disease as compared to milder COVID-19 infection probably as a fallout of the cytokine burst and immune dysregulation [15].

Obesity is known to be a poor prognostic marker for various critical illness including AP, because of the increased risk for development of organ failure [22,23]. Obesity entails increased visceral adipose tissue [24], including intra-pancreatic fat (IPF). On release of pancreatic enzymes during an episode of AP, unsaturated fatty acids (UFAs) of the triglycerides in the adipocytes get released by hydrolysis and perpetuates fat necrosis in AP. The unbuffered portion of the released UFAs leads to cytokine burst, organ failure and end-organ damage. A similar pathogenetic mechanism of cell injury by UFAs has been recently described in COVID-19 infection and has been found to be linked to mortality [25]. Additionally, obesity has been shown to be a risk factor for poor prognosis in COVID-19 infection [26]. Moreover, as mentioned earlier, ACE2, expressed both in adipose tissue and pancreas [15,27], is a key receptor for the virus. Thus, this pathway of virus induced lipotoxicity and cytokine storm [28] can explain the pancreatic injury. In fact, the cytokine profile of both AP and COVID-19 infection has been found to be similar, with increased levels of IL-6, IL-8 and IL-10 [29].

In the earlier studies, SARS-CoV had been shown to cause higher fasting plasma glucose levels [30] and the damage of the pancreatic beta cells was incriminated as a cause for development of "acute diabetes" [31]. The virus can also affect the glucose regulation through the Na^+/H^+ exchanger (NHE) and lactate pathways [32]. When ACE2 is blocked, angiotensin II levels increase which activate NHE. This can lead to cellular hypoxia and generation of reactive oxygen species resulting in endothelial damage and insulin resistance. Additionally, infection of the exocrine pancreas can lead to collateral damage to beta cells via inflammatory cytokines [33].

Thus, damage to the pancreas, both exocrine and endocrine, is multifactorial: i) direct virus mediated injury of the exocrine pancreas through the ACE2 receptors; ii) severe COVID-19 infection can lead to systemic inflammation and pancreatic injury; iii) virus mediated injury to the islet cells; iv) damage by pro-inflammatory milieu through high levels of interleukin-1β, Monocyte Chemoattractant Protein (MCP)-1 etc and immune dysregulation; v) virus-induced lipotoxicity from UFAs causing hyperlipasemia; v) drug-induced pancreatic injury (due to non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids).

Real world data of COVID-19 and pancreatic injury

Although mechanistically, there is a reason to believe that SARS-CoV-2 can cause significant pancreatic injury, the real-world data are quite contrasting. There are only a few studies looking into evidence of pancreatic injury in a cohort of proven COVID-19 patients while the remaining are case reports of evident pancreatitis in COVID-19 patients.

a) Observational case-control studies on pancreatic injury

Limited studies have looked into the prevalence of pancreatic injury in COVID-19 patients (Table 1). Various studies have defined pancreatic

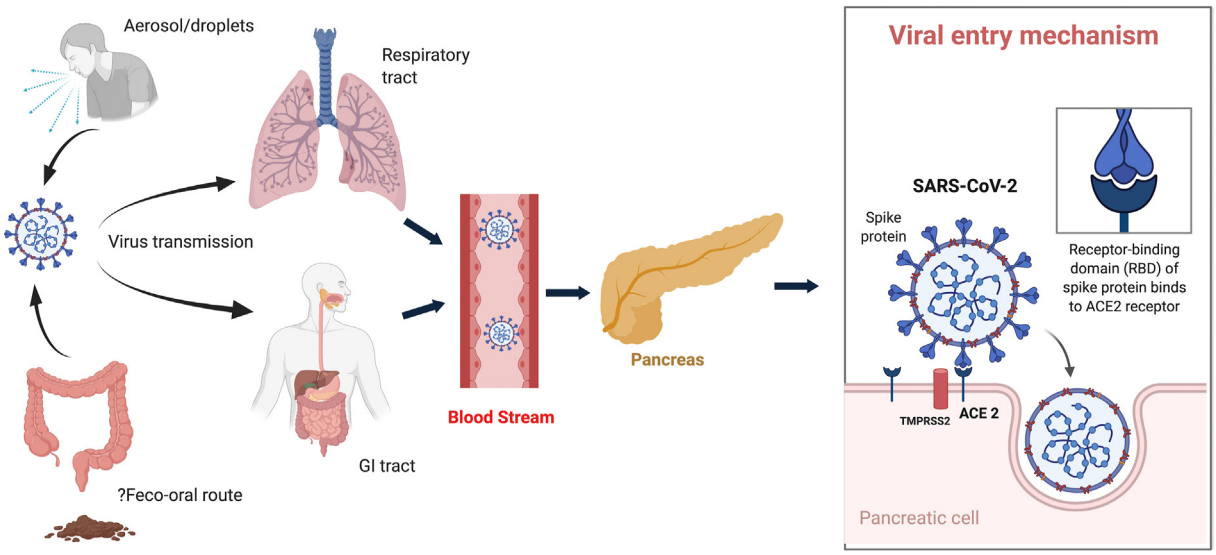

Fig. 1. Schematic diagram showing transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the pancreas and mechanism of the virus entry. TMPRSS, transmembrane serine protease; ACE2, angiotensin receptor 2.

injury differently. Most of the authors have defined the pancreatic abnormality as elevation of serum amylase/lipase levels above the normal limit. Imaging findings in the form of computed tomography (CT) abnormalities have been reported by only some studies.

Laboratory abnormalities suggestive of pancreatic injury have been noted in 8.5%–17.3% of cases [15,34–37] in various studies. Overall 51 (12.8%) of the 397 reported patients had pancreatic injury. Acute pancreatitis (AP) is defined when two of the following three features are met: i) pancreatic type abdominal pain; ii) serum lipase/amylase more than three times the upper limit of the normal (ULN); iii) characteristic imaging findings of AP on CT/MRI/ultrasonography [38]. However, using these criteria, only 3/397 (0.76%) patients had features of clinical AP. In fact, McNabb-Baltar et al. [35] pointed out that although 12.1% cases had raised lipase, only 2.8% (2/71) had levels more than 3 times the ULN. Moreover, 6/13 patients in the study by *Liu* et al. [15] and 7/9 patients in the report by Wang et al. [36] had concomitant drug history (corticosteroids and NSAIDs). Liu et al. [15] reported that only 5/13 cases (overall 4.13%) with pancreatic injury had abnormal CT findings in the form pancreatic enlargement and none of them had pancreatic necrosis. McNabb-Baltar et al. [35] had pointed out that none of the cases, where imaging was done, showed any feature characteristic of AP.

Interestingly, pancreatic abnormalities have been more frequently noted in the sub-group of patients having severe COVID disease (Table 1). Liu et al. [15] showed that 17.9% of cases had raised amylase in the severe group compared to only 1.85% among non-severe cases. Looking at data from three studies, 20 (22%) of the 91 severe cases had pancreatic abnormalities [15,35,36]. Barlass et al. [37], on multivariate analysis, showed that elevated lipase level was associated with a significantly increased need for ICU

Table 1
Studies showing incidence of pancreatic injury in COVID-19 patients.

Study (country)	No. of patients with pancreatic injury/Total no. of patients	Raised amylase	Raised Lipase	Pain abdomen (pancreatic)	CT/imaging findings	Severe disease with injury	Remarks
Liu et al.[15]**(China)**	13/121 (10.74%)	13/121 (10.74%)	12/121 (9.92%)	3/13	Normal - 8 (3.62%); Enlargement - 5 (4.13%); Necrosis - 0	12/67	Non-severe cases: 1.85%; Severe - 17.9%; NSAIDs - 2, Corticosteroids - 4
Bruno et al.[34]**(Italy)**	6/70 (8.5%)	6/70 (8.5%)	6/70 (8.5%)	None	Normal CT in one case	5/6	Pancreatic abnormality in one case at admission; Associated GI symptoms in all; No definite clinical AP
McNabb-Baltar et al.[35]**(USA)**	9/71 (12.1%)	..	9/71 (12.1%); 2/71 (2.8%) had levels >3*ULN	None	No evidence of pancreatitis	4/9 (44.4%)	Associated GI symptoms; No clinical AP
Wang et al.[36]**(China)**	9/52 (17.3%)	7/52 (13.5%)	5/52 (9.6%)	None	..	4/9 (44.4%)	7/9 patients - corticosteroids; No definite clinical AP
Barlass et al. [37] (USA)	14/83 (16.8%)	..	14/83 (16.8%)	None	..	13/14 (92.9%)	Elevated lipase associated with increased ICU admission and intubation

COVID-19 Coronavirus disease 2019; CT Computed tomography; NSAIDs Non-steroidal anti-inflammatory drugs; GI Gastrointestinal; ULN Upper limit of normal; AP Acute pancreatitis; ICU Intensive care unit.

admission and intubation. Additionally, most of the studies have found that a majority of patients with reported pancreatic abnormalities had GI symptoms such as nausea, anorexia, abdominal discomfort (not pain) and diarrhea [34–36].

b) Case reports/series of acute pancreatitis with COVID-19

Multiple case reports and a few case series have reported clinical AP in the setting of COVID-19 infection (Table 2). Most of these cases had severe COVID-19 infection at baseline. However, a few of these cases had no respiratory symptoms to start with [39–41]. One of the initial reports was that of development of AP in 2 out of 3 COVID-19 positive hospitalized members of a family in Denmark [42]. Alloway et al. [39] reported a case of a 7-yr-old girl with AP without any respiratory symptoms at onset. On evaluation, she was found to be COVID-19 positive. Stevens et al. reported a 10-yr-old female child presenting with AP who progressed to develop multisystem inflammatory syndrome of children, secondary to COVID-19 infection [43].

There are reports of development of AP in patients of COVID-19 infection having respiratory symptoms as well as reports of patients with AP developing hospital acquired COVID-19. Rabice et al. [44] reported a case of a 36-yr-old pregnant female with respiratory symptoms followed by development of clinical AP and she was found to be COVID-19 positive. Cheung et al. [45] reported an interesting case of recurrent AP, probably secondary to COVID-19 infection. Schepis et al. [46] described an intriguing finding of SARS-CoV-2 positivity in pancreatic pseudocyst sample of a follow-up case of AP presenting with pain abdomen and chest infiltrates. This finding is interesting as SARS-CoV-2 has already been detected in various body fluids such as urine and blood besides respiratory aerosols. The finding of the virus in pseudocyst fluid hints to the fact that the virus might be detected in other body fluids as well, and hence to chances of transmission.

In a cohort of 35 proven AP patients, Szatmary et al. [47] found 10 cases with SARS-CoV-2 positivity of whom 5 had no definite etiology and were attributed to COVID-19 infection. In a study by Elhence et al. [48], 3 cases of hospitalized AP patients developed nosocomial COVID-19 infection, but none had worsening of the disease. However, a recent study, that has compared AP patients with and without COVID-19 infection, revealed contrasting results. COVID-19 patients with AP had significantly higher requirement of mechanical ventilation and length of hospital stay compared to the COVID-19 negative ones. Interestingly, 69% of the COVID positive AP cases had idiopathic pancreatitis compared to 21% of the COVID-19 negative AP [49]. Similar findings were voiced by Dirweesh et al. [50], with higher rates of organ failure and mortality in the cohort of COVID-19 positive AP cases when compared to COVID-19 negative patients.

c) COVID-19 infection with past history of pancreatitis

Pancreatitis, acute or chronic, is known to increase morbidity and often have nutritional deficiencies which might lead to compromised immune systems. Gubatan et al. [62], in an interesting study, found that the prevalence of COVID-19 infection in patients with prior pancreatitis was 7.8% compared to 2.8% of the general population. In multi-variate analysis, idiopathic pancreatitis was found to be an independent risk factor for COVID-19 infection. Interestingly, none of the patients with past history of pancreatitis developed AP during the COVID-19 infection [62].

Table 2
Case reports/series of acute pancreatitis with COVID-19 infection.

Study (country)	Type of study	Raised amylase/lipase	pain abdomen	CT/imaging findings	Remarks
Mierles et al. [51](Portugal)	Case report	+	+	Normal	Clinical AP
Hadi et al. [42](Denmark)	Case series	+	+ (1/2)	1 had voluminous pancreas on USG	2 out of 3 members of the family had AP
Aloysius et al. [52](USA)	Case report	+	+	Normal	Clinical AP
Alloway et al. [39]	Case report	+	+	suggestive of necrotising pancreatitis	7-yr-old girl with AP; No respiratory symptoms to begin with
Miao et al. [41](France)	Case report	+	+	Enlarged pancreas	No respiratory symptom with clinical AP
Anand et al. [53](UK)	Case report	—	+	Edematous pancreas	Clinical AP
Pinte et al. [54](Romania)	Case report	+	+	Edematous pancreas	Clinical AP
Schepis et al. [46](Italy)	Case report	—	+	Pseudocyst of pancreas	Cyst fluid positive for SARS-CoV-2
karimzadeh et al. [40](Iran)	Case report	+	+	Normal	No respiratory symptoms
Rabice et al. [44](USA)	Case report	+	+	Not done	Pregnant female with Clinical AP
Morrison et al. [55](USA)	Case report	+	—	Not done	Tocilizumab induced hypertriglyceridemia; 1 case had AP
Szatmary et al. [47](UK)	Case series	—	+	Mild edematous pancreas	5 cases attributed to COVID in a cohort of 35 proven AP
Elhence et al. [48] (India)	Case series	+	+	Necrotising pancreatitis	3 cases had nosocomial COVID infection in proven AP while 2 had AP with COVID infection at diagnosis
Cheung et al. [45]	Case report	+	+	Suggestive of AP	Reported case of recurrent AP secondary to COVID-19
Stevens et al. [43] (USA)	Case report	+	+	Suggestive of AP	10-yr-old female with AP, later developing MIS-C
Bokhari et al. [56] (Pakistan)	Case report	+	+	Bulky pancreas with peri-pancreatic inflammatory fluid	Clinical AP
Gonzalo-Voltas et al. [57] (Spain)	Case report	+	+	Consistent with AP	Clinical AP
Mazrouei et al. [58] (UAE)	Case report	+	+	Edema of pancreas with fluid collection	Clinical AP
Brikman et al. [59] (Israel)	Case report	+	+	Evidence of pancreatitis	Clinical AP; patient received antecedent tocilizumab, dexamethasone.
Kataria et al. [60] (USA)	Case report	+	+	Edematous pancreas	Clinical AP
Gadiparthi et al. [61] (USA)	Case report	+	+	Peripancreatic stranding with fluid	Clinical AP with antecedent hypertriglyceridemia and type 2 diabetes

AP acute pancreatitis; COVID Coronavirus disease; SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2; MIS-C Multisystem inflammatory syndrome of children.

d) Autopsy data of pancreatic injury

While majority of the autopsy data in COVID-19 have described lung findings, data on pancreatic injury is limited. In an autopsy series of 3 COVID-19 cases by Yao et al. [63] it was noted that only a few islet cells were degenerated while the exocrine pancreas had no abnormality and was negative for SARS-CoV on immunohistochemistry. On the contrary, using a murine monoclonal antibody, Ding et al. [64] demonstrated that SARS-CoV-2 could be detected in multiple organs including the pancreas in 4 autopsy cases of COVID-19 related death. Lax et al. [65] in another autopsy study, pointed out that 5 out of 11 cases (45.5%) had focal pancreatitis, although none had clinical suspicion of pancreatitis. This high proportion of focal pancreatitis could be part of end-organ damage rather than the actual virus inflicted injury. In another autopsy series, 2 (25%) of the 8 cases had pancreatic abnormalities. One 22-yr-old man had haemorrhagic, necrotic changes while another 97-yr-old man had microscopic evidence of pancreatitis [66].

Clinical implications of the available data

Since viral infections are known to cause pancreatitis [5] and pain abdomen has been a well reported GI symptom among COVID-19 patients [67], the association of COVID-19 infection with pancreatic injury/inflammation seems logical. However, a critical analysis of the available data cast doubts on this probable association. As pointed out earlier, most of the cohort studies have used mere elevation of serum amylase/lipase levels as surrogate markers of pancreatic injury. Moreover, only a fraction (2.8% in one study) of these patients had levels >3 times ULN and practically none had robust evidence of clinical AP as per the diagnostic criteria [38]. Raised serum amylase levels are not specific for AP and can have different sources including the healthy and diseased lung [68]. Lipase is more specific for diagnosing AP but is not exclusive. Lipase levels can be elevated because of various other conditions such as underlying diabetes or renal dysfunction [69], critical illness [70] or drugs such as corticosteroids [71]. All of these factors are commonly encountered in COVID-19 positive patients.

Since GI involvement in COVID-19 is well documented, increased intestinal permeability secondary to SARS-CoV-2 infection can lead to increased pancreatic enzyme levels [72]. Gastroenteritis is also known to cause hyperamylasaemia [73]. Interestingly, COVID-19 patients with pancreatic abnormalities, as mentioned above, had higher prevalence of GI symptoms. Thus, GI involvement, by itself, can explain the isolated rise in the amylase/lipase without associated pancreatitis in this group of patients.

Elevated pancreatic enzymes or AP can also be secondary to cytokine storm and multi-organ dysfunction leading to pancreatic injury rather than the direct cytopathic effects of the virus. Mechanical ventilation or shock, too, can lead to hypoxic pancreatic damage [74]. This corroborates with the evidence that pancreatic injury was higher among patients with more severe disease.

Multiple drugs such as corticosteroids and NSAIDs used during management of COVID-19 can precipitate pancreatitis [75]. Many of the case series and reports highlighted above had antecedent history of these drugs which may account for the rise of pancreatic enzymes rather than it being the effects of the virus. Additionally, drugs such as tocilizumab (TCZ) and lopinavir/ritonavir can lead to hypertriglyceridemia. This in turn can result in pancreatitis as well. Morrison et al. have reported one case of TCZ-induced hypertriglyceridemia related AP [55]. Similarly, Baricitinib, a drug used for COVID-19 treatment can lead to AP as well [76]. Thus, drugs are an important contributor for pancreatic injury among COVID-19 patients. Conversely, high dose steroids used for conditions like autoimmune pancreatitis (AIP) can theoretically pose high a risk for poor outcome in COVID-19 infection. However, Liaquat et al. [77] have reported favourable outcome of COVID-19 infection in a case of AIP treated with steroids. Data on actual risk is lacking, but it would be advisable to shorten the induction schedule for steroids and reduce azathioprine in case of lymphopenia for AIP [78].

As very few cohort studies exist on the prevalence of pancreatic injury/inflammation among COVID-19 patients, a possibility of under reporting may also need consideration. A lot of additional questions remain unanswered for COVID-19 related AP such as: i) timing of onset of AP from the time of infection; ii) disease course; iii) assessment of disease severity in the background of COVID-19 related symptoms; iv) overall outcome of concomitant AP with COVID-19 infection. Thus, more robust data and national/international registries are required for better understanding of this conundrum of COVID-19 infection and pancreatic injury.

Pancreatic endocrine system and COVID-19

The interaction of COVID-19 with pancreatic endocrine system complicates the scenario for patients with diabetes mellitus (DM) infected with the virus. DM with associated hyperglycemia has been found to have poor prognosis with increased morbidity and mortality [79,80]. This can be explained to be secondary to depressed innate immune response and exaggerated cytokine response in DM [81]. Moreover, the severity of the infection is related to the concentration of glycosylated ACE2 receptors in pulmonary epithelium. Thus, increased receptors in lung of individuals with uncontrolled DM can perpetuate binding of the virus and in turn cause severe disease [80]. Conversely, COVID-19 infection can worsen the glycaemic control through damage to the pancreatic beta cells either directly by SARS-CoV-2 or via cytokine mediated damage. The complex interplay of DM and COVID-19 is beyond the scope of this article and hence not discussed in much details here.

Pancreatic cancer and COVID-19

Presence of comorbidities not only pre-disposes to increased likelihood of being infected with COVID-19 but also leads to a more severe disease course [79]. Cancer has been found to be a risk factor for increased likelihood of infection and also severe disease [82], more so with lung and colorectal cancer [83]. In one study, pan-cancer analysis showed pancreatic adenocarcinoma to have increased ACE2 expression [84], and deep deletions for TMPRSS2 [85]. This may hint towards increased baseline risk in this group of patients. Moreover, chemotherapeutic drugs, when used for management of pancreatic cancer, cause immunosuppression leading to added risk. A very high rate (40%) of adverse events and complications has been reported with chemotherapeutic regimens in COVID-19 patients [86].

Pancreatic cancer, as such, has a very dismal prognosis. The added risk of this pandemic warrants more careful assessment of the risk-benefit ratio. While major pancreatic onco-surgeries have a high morbidity and complications rate, chemotherapy treatment can compound the risk. Thus, the decision for medical and surgical therapy needs to be tailor made after a multi-disciplinary team consultation [87,88]. A tiered approach has been advocated to prioritise various interventions for optimum benefit: i) tier 1 (high priority) includes life threatening conditions or where there is significant improvement in the survival; ii) tier 2 (medium priority) encompasses condition where a 6–8 weeks delay would not hamper the overall outcome; iii) tier 3 (low priority) entails stable patient conditions wherein services can be delayed for the pandemic to be over or situation where there will be no survival gain. European Society for Medical Oncology (ESMO) [89] and other societies

Panel 1
Key recommendations for the management of pancreatic cancer during COVID-19 pandemic

- **Outpatient visit priorities**
  - Patients with newly diagnosed resectable cancer to be consulted on high priority, preferably through telemedicine, along with multi-disciplinary assessment for plan for surgery.
  - Unstable patients or those requiring interventions such as jaundice, cholangitis, post-surgical complications etc to be given priority
  - Patients with established diagnosis with minor problems should be directed towards telemedicine.
  - Post-operative patients with no complications or with no issues should be discouraged from OPD visits.
- **Imaging priorities**
  - Symptomatic patients, such as jaundice or intestinal occlusion should be given priority
  - For diagnosis of pancreatic cancer, CT followed by EUS, if resectable, need to be considered
  - Routine follow up for recurrence or restaging after surgery needs to be kept on low priority
- **Surgical oncology and endoscopic intervention procedures**
  - Resectable malignancy including cystic lesions with suspicion of malignancy to be kept high priority
  - Endoscopic stenting for biliary obstruction, cholangitis, or for those planned for neoadjuvant/palliative treatment should be carried out on high priority
  - Post-surgical complications to be managed promptly
  - For non-resectable diseases/metastatic diseases with life expectancy >3 months, biliary or duodenal obstruction can be managed with hepatojejunostomy/hepatogastrojejunostomy/endoscopic stenting can be done with lower priority
- **Medical oncology priorities**
  - For localised or locally advanced disease
    - o Initiation or completion of neoadjuvant/adjuvant treatment with high priority
    - o Adjuvant treatment to be initiated with ECOG PS 0, <70 yrs old, based on pathologic state and individual risk assessment
    - o Modified FOLFIRINOX regimen to be considered, and delaying treatment up to 12 weeks after surgery
    - o Follow up imaging or restaging in asymptomatic cases to be deferred
  - For advanced/metastatic disease
    - o First line chemotherapy likely to improve survival in patients who can tolerate combined regimen
    - o Monotherapy regimen for asymptomatic/oligo-symptomatic cases to be assessed based on the risk-benefit ratio
    - o Follow-up imaging/restaging studies to be deferred
    - o Anti-resorptive therapy such as zolendronate to be deferred
  - Prophylactic use of G-CSF for minimising neutropenia-associated risks is debatable
  - Adequate venous thromboprophylaxis to be provided

COVID-19 Coronavirus disease 2019; OPD outpatient department; EUS endoscopic ultrasonography; ECOG Eastern Cooperative Oncology Group; PS Performance Status; G-CSF Granulocyte colonystimulating factor

including National Cancer Institute of Milan [90] have come up with recommendations for management during this pandemic. A synopsis of the recommendations has been outlined in panel 1.

Pancreatic surgery and COVID-19

Surgery, specifically pancreatic, uses up an immense amount of hospital resources in the form of logistics, health care workers, time and adnexal support requirements. American College of Surgeons (ACS) guidelines have defined the type of surgery that can be performed depending on the phase of the pandemic [91]. As most countries are now in the phase II/III of the pandemic, patients requiring surgery within hours to within a few days are the ones that can be taken up for surgery, keeping the rest at bay. Worldwide surveys have shown a reduction in the rates of pancreatic surgeries. In a survey of 267 centres spanning 37 countries, Oba et al. showed that while in most centres, the weekly pancreatic resections decreased from a median of 3 to 1, the remaining centres (30.7%) did not perform any pancreatic surgery at all [92]. A European-African Hepato-Pancreato-Biliary Association (E-AHPBA) survey revealed that most centres had reduction in the number of surgeries including cancer surgery due to inadequate ICU beds and the fear of post-operative COVID infection [93]. Non-essential surgeries were not carried out by 83% of the respondents. In fact, in COVID-high countries, chemotherapy was preferably used over surgery even for resectable pancreatic cancer.

Surgery for potentially curable pancreatic adenocarcinoma and pancreatic cystic lesions with high grade dysplasia are advocated (Panel 1). Pre-operative testing for COVID-19 has been advocated. All suspected and confirmed cases are to be transported by dedicated medical staff with adequate precautions by the shortest possible route. For confirmed cases, dedicated operating theatres with negative pressure facilities or an air exchange rate of $\geq$25cycles/hour are recommended. A Joint statement from ACS recommended that resumption of elective surgeries can be done only when there is sustained reduction in the new COVID-19 cases in that geographical location for at least 14 days and there is adequate logistic back-up to cater to non-elective cases [94].

Pancreatic transplant recipient and COVID-19

Limited data exist on the effects of COVID-19 infection on pancreatic transplant recipients. Dube et al. [95] reported the first case series of 4 simultaneous kidney-pancreas transplant (SPK) recipients, of whom 1 died while the remaining cases improved. Suwanwongse et al. [96] described a case of SPK on immunosuppressants developing COVID-19 infection and respiratory failure with fatal outcome. A Swiss Transplant Cohort study [97] of 21 cases of solid organ transplant recipients included 1 pancreatic and 2 SPK recipients. Most of them presented with classical COVID-19 symptoms, of which 1 SPK recipient required ICU admission, but without any mortality. Transplant recipients are on long standing immunosuppressants and theoretically are at an increased risk for COVID-19 infection and possible severe disease course. More data is warranted before the actual risk or the course of COVID-19 infection in these sub-group of patients can be optimally assessed.

Pancreatic endoscopy during the COVID-19 pandemic

Pancreatic endoscopy, in the wake of the COVID-19 pandemic,

is a debatable option that the endoscopist needs to assess considering all the pros and cons. Endoscopy, being an aerosol generating procedure, poses a high risk for the operating endoscopist and assisting technical staff [98]. The possible routes of transmission during an endoscopic procedure can be person to person, droplet mode, aerosols generated in the positive pressure room, and contact with contaminated bodily fluids and faecal matter [99]. The risk of transmission enhances manifold due to multitude of factors: i) aerosols from the patient's respiratory secretions contaminates the endoscopy room, more so when the viral load is high; ii) endoscopic procedures are high aerosol generating procedures, because of coughing and retching during upper GI endoscopy and passage of flatus during colonoscopy; iii) Suctioning and exchange of accessories during endoscopy pose further risk by splashing and spreading of infective material [100,101]. Pancreatic endoscopy entails endoscopic retrograde cholangiopancreatographies (ERCPs) and endoscopic ultrasounds (EUS). Both these procedures may pose still higher risk due to larger scope diameter, longer procedure time and higher need for exchange of accessories during the procedure. Thus, for all interventions, a triaging system is essential to optimise patient care and minimise health care worker risk.

Endoscopists need to assess the following: i) need for the procedure – risk benefit ratio; b) if the procedure is time sensitive, then whether it is urgent (<2weeks) or semi-urgent (2–8 weeks); iii) if the procedure can be deferred beyond 8 weeks [102]. Important parameters that need to be reviewed include threat to patient's life, risk of disease progression/worsening or risk of metastasis. Thus, ERCP for obstructive jaundice or cholangitis, EUS guided drainage for infected/symptomatic pancreatic fluid collection or for fine needle aspiration/biopsy for pancreatic lesion/cyst without metastatic lesions may be carried out on a priority basis [103]. Endotherapy for chronic pancreatitis, celiac plexus block, evaluation for idiopathic/recurrent pancreatitis etc. can be deferred. The precautions to be taken during the procedure have been outlined in various society guidelines.

Conclusion

Although mechanistically SARS-CoV-2 is expected to cause pancreatic injury, robust real-world data on its actual impact is lacking. The elevation of serum levels of pancreatic enzymes, amylase and lipase, has been considered as a marker of pancreatic injury and attributed to the effect of COVID-19 infection. However, actual evidence of clinical pancreatitis secondary to SARS-CoV-2 is dubious. Whether this reported pancreatic enzyme elevation in COVID-19 positive patients, more for severe cases, has a cause-effect relationship or just an epiphenomenon needs to be established. Larger data and international registries focused on this aspect can possibly give an answer. Pancreatic cancer management and pancreatic surgeries in this COVID era have to be tailor made to individual cases after multi-disciplinary assessment of the available options and the risk-benefit ratio. Interventions including pancreatic endotherapy not only burdens the over-stretched health system in this COVID era, but also increases risk for health care workers. Thus, triaging of cases and catering to only the essential ones are recommended. Adequate precaution, avoiding elective cases, and "lying low" in terms of interventions are the key strategies that will enable the gastroenterologists and pancreatologists to tide over this COVID-19 crisis.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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