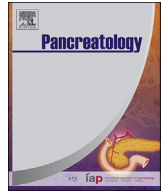




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## SARS-COV-2 associated acute pancreatitis: Cause, consequence or epiphenomenon?



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Dear Editor,

The rapid spread of a novel coronavirus disease (COVID-19) caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2) has triggered a global pandemic. With most patients presenting with respiratory symptoms, there is a relative paucity of knowledge about the impact of COVID-19 on the gastrointestinal tract. In the early phases of the pandemic, there appeared to be no known link between the SARS-CoV-2 virus and the pancreas. Since then, however, there have been several reports of acute pancreatitis (AP) in COVID-19 patients.

Wang et al. were the first to describe this in a case series of 52 patients, 9 of whom were diagnosed with AP [1]. Another study found elevated amylase and lipase levels in 12 of 64 patients with severe COVID-19 infection [2]. The severity of AP observed varies from mild [1,2] to severe [3] but unfortunately accepted diagnostic criteria [4] was not used in these studies, raising the possibility that the elevated pancreatic enzymes may be due to other causes including increased gut permeability with SARS-CoV-2 infection [5]. Not only is there the possibility of over-reporting SARS-CoV-2 associated AP, there could also be under-reporting. The recently formed Consortium for Clinical Characterisation of COVID-19 comprising 96 hospitals across five countries has generated a database of anonymised electronic health records from 21,324 patients [6]. Of the 34 patients with a diagnosis of AP, 24 did not have a stated cause. Further, 20% of patients with COVID-19 infection present with abdominal symptoms and a proportion of these may represent a missed diagnosis of AP, especially when attention is diverted to the management of critically ill patients with multiple organ failure.

Not only is there uncertainty about the incidence of SARS-CoV-2 associated AP but there are also questions about its clinical features and pathogenesis. We do not know the timing of AP in relation to SARS-CoV-2 inoculation or the natural history and clinical trajectory of SARS-CoV-2 associated AP. It is not known whether currently accepted prognostic scoring systems for AP are appropriate, whether there is a heightened pro-inflammatory response, or whether the risk of organ dysfunction (especially acute respiratory distress syndrome) is compounded and/or more severe. When

available, it will be interesting to study the impact of future vaccines and novel therapeutics designed for SARS-CoV-2 on the clinical course of AP.

Acute pancreatitis associated with viral infections, most commonly the hepatitis B virus and Coxsackie B virus, is well described [7]. The mechanism by which AP develops following viral infections varies depending on the type of virus involved [7]. SARS-CoV-2 is known to enter cells by binding to the receptor proteins ACE2 and TMPRSS2. A study from 2010 using immunostaining found ACE2 to be highly expressed in islet cells and postulated that binding of SARS-CoV caused islet cell injury and hyperglycaemia in infected patients [8]. Single-cell RNA sequencing has been used to evaluate their expression, but there is conflicting data with one study reporting high expression within ductal and acinar cells [3], while another study found no significant expression in the pancreas [9]. It is not known whether SARS-CoV-2 causes AP, whether the AP is a consequence of severe systemic inflammation and microvascular thrombosis from COVID-19 infection, or whether it is just an epiphenomenon.

More data about SARS-CoV-2 associated AP is needed from both the laboratory and the clinic. One way forward might be to use a pancreas organoid model to study the pancreas-specific effects of SARS-CoV-2, analogous to the intestinal organoid model used to study enteric infections [10]. There is also an urgent need for more international collaboration to pool clinical and scientific experience about SARS-CoV-2 associated AP, to better understand it and to improve the management of these patients.

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