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Mild Pancreatic Enzyme Elevations in COVID-19 Pneumonia: Synonymous With Injury or Noise?

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Dear Editors:

We read the article[1] by Dr Wang and colleagues with interest. They suggest that pancreatic enzyme elevations signify pancreatic injury due to cytotoxic effects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Although preliminary data[2] suggest that the transmembrane protease serine 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2), which mediate cellular entry of SARS-CoV-2, are found on pancreatic ductal cells, the pathologic consequences of this are not clear at the current time. The use of serum pancreatic enzyme elevations to delineate the presence or degree of pancreatic injury is not validated or recommended, for example, in asymptomatic patients for monitoring of checkpoint inhibitor–induced pancreatic toxicity[3] or for determining the degree of pancreatic injury in trauma patients.[4]

The clinical significance of serum amylase and lipase elevations primarily centers on their role in diagnosing acute pancreatitis. In the absence of imaging, none of the 9 patients in this series met the revised Atlanta classification criteria for acute pancreatitis, as there was no report of abdominal pain and the pancreatic enzymes were not above 3 times the upper limit of normal (ULN). Serum lipase is widely recommended over amylase for diagnosing acute pancreatitis because of its improved sensitivity. Therefore, any potential clinical merits of this study lie primarily in those 5 patients (cases 1, 4, 5, 8, and 9) with elevated lipase levels. However, lipase can be elevated without obvious major clinical sequelae for a variety of reasons not related to direct cytotoxic effects of SARS-CoV-2, including intensive care unit critical illness (case 4), diabetes (cases 1 and 5), and opioid use (not detailed).[5–7] Of the 5 cases of mildly elevated lipase, only 2 (cases 8 and 9) do not have obvious alternative explanations as delineated previously, and the lipases in those cases are 85 and 77 U/L (ULN was 70 U/L), respectively. This could be within the margin of error for the laboratory assay. Our own laboratory, for example, has a serum lipase ULN of 63 U/L with a 10% margin of error (personal communication, 2020); therefore, the application of this margin of error to case 9 would bring their lipase into the normal range. We would also point out that 7 of the 9 patients received corticosteroids (cases 1, 3, 4, 5, 6, 7, 8), which has been associated with elevated lipase levels.[8]

In summary, most of the patients in the study by Wang et al.[1] have alternative explanations for their lipase elevations besides SARS-CoV-2 infection, and the mild enzyme elevations themselves are of equivocal clinical significance. Future studies are needed to evaluate if SARS-CoV-2 infection of pancreatic cells leads to injury on a mechanistic level before translation to clinical practice settings.

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Conflicts of interest
Vikesh K. Singh is a consultant for AbbVie and Theraly, medical advisory board participant for Cook Medical, and receives grant support from Orgenesis. These financial interests do not pertain directly to this work. The remaining authors disclose no conflicts.

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Reply. We read with great interest the letter by Dr Enrique de-Madaria et al[1] and Dr Aditya Ashok.[2] de-Madaria et al[1] highlighted that the definition of pancreatic injury in our study lacked specificity, because many factors could lead to increased pancreatic enzyme (PE) levels, not just pancreatic injury. Ashok et al[2] indicated that it was not recommended to use the serum PE elevations to delineate the presence or degree of pancreatic injury.[2] They all mentioned that none of our cases met the revised Atlanta classification criteria for acute pancreatitis. Indeed, our study mainly proposed and emphasized the potential pancreatic injury caused by the novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]).[3] Because it was reported for the first time, the underlying mechanism confused us until now.

Currently, several studies have focused on pancreatic injury in patients with Coronavirus Disease 2019 (COVID-19). Naren et al[4] reported the occurrence of acute necrotizing pancreatitis in a patients with COVID-19 in the absence of any known risk factors. Severe acute

pancreatitis was also found in 2 family clusters with SARS-CoV-2 infection.[5] Furthermore, SARS-CoV-2 RNA was detected in the pancreatic pseudocysts of a patients with COVID-19.[6] In the Giuseppe et al[7] study of 70 COVID-19 cases, 6 (8.5%) demonstrated pancreatic abnormalities with significant evaluations of serum PE activity. Mechanistically, it had been found that angiotensin-converting enzyme 2 (ACE2), receptor of SARS-CoV-2, was more highly expressed in the pancreas than the lungs.[8] Studies further demonstrated that ACE2 and transmembrane serine protease 2 were prominently expressed in pancreatic ductal epithelium and microvasculature.[9,10] Moreover, the autopsies of 3 COVID-19 cases showed degeneration of islet cells.[11] In addition, ACE2 and transmembrane serine protease 2 were found to be highly expressed in gastrointestinal epithelial cells, and the virus could be detected in stools. Thus, SARS-CoV-2 might infect the pancreas by spreading from duodenal epithelium to pancreatic ductal epithelium. Most importantly, during the outbreak of another coronavirus (SARS-CoV) in 2003, its antigen and RNA were detected in pancreatic cells.[12] Collectively, these results indicated the pancreas as a potential target of SARS-CoV-2.

In addition, viral sepsis was hypothesized in the COVID-19 progression.[13] Severe SARS-CoV-2 infection could cause alveolar macrophages or epithelial cells to produce various proinflammatory cytokines and chemokines and led to uncontrolled inflammation cascade and cytokine storm. Meanwhile, severe endotheliitis directly induced by SARS-CoV-2 could further cause diffuse microischemic disease in the pancreas.[14] Thus, the disseminated SARS-CoV-2 could also directly attack multiple other organs, including the pancreas. Eventually, viral sepsis, ischemic damage, and multiple organ failure occurred. Furthermore, up to 16% of patients with severe COVID-19 had elevated PE levels and 7% showed significant changes in the pancreas on computed tomography, but fewer than 2% in patients with non-severe COVID-19.[8] Taken together, we must pay attention to potential pancreatic injuries during the management of COVID-19.

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The Courage to Return to Everyday Life at the Time of COVID-19: The Point of View of Inflammatory Bowel Disease Patients Needing Endoscopy

Dear Editors:

We read with interest the paper by Rex et al[1] on the willingness of patients to undergo elective endoscopic procedures after lockdown due to the Coronavirus Disease 2019 (COVID-19) pandemic. The authors reported that only 4.3% of surveyed patients were unwilling to undergo elective endoscopy in May 2020. Due to the COVID-19 pandemic, there was a huge increase in the number of hospitalized patients, which overloaded health systems and caused the dramatic shortage of health resources[2] and the consequent scarcity of medical assistance among acute and chronic diseases. This led to a forced stop or a significant limit on health system offer, including elective outpatient endoscopic procedures also in patients with inflammatory bowel diseases (IBD).[3] Alternative methods of disease assessment, including biomarkers or telephone/email helpline to support patients with disease flares, were suggested.[3] These restrictive measures help to keep patients at home but may lead to an excessive use of corticosteroids, which could worsen the course of any eventual COVID-19 infection,[4] or they could delay the start of biological therapies with related consequences.[5] As it is uncertain how long the COVID-19 pandemic will last, we do not know if a prolonged period without endoscopy may result in long-term implications for patients with IBD who need to monitor efficacy of treatments or be screened for dysplasia and colorectal cancer.[6] Therefore, a gradual return to routine