

Insights into Acute Pancreatitis Associated COVID-19

Subjects: **Gastroenterology & Hepatology**

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Pancreatic injury can manifest from an asymptomatic elevation of amylase and lipase to severe acute pancreatitis (AP).

acute pancreatitis

coronavirus disease 2019

1. Background

Acute pancreatitis associated with coronavirus disease 2019 (COVID-19) has been widely reported. Recent studies have discussed pancreatic compromise incidentally in asymptomatic patients, or in a form of clinical symptoms such as abdominal pain, nausea, or vomiting, which is further reflected in some cases with abnormal serum lipase and amylase levels. It was suggested that upregulation of angiotensin-converting enzyme II cell receptors or inflammatory cytokines play a major role in predisposing pancreatic injury in SARS-CoV-2 positive patients. To date, there is insufficient data to establish the causality of acute pancreatitis in SARS-CoV-2 infected cases.

2. Current Insight Into Acute Pancreatitis Associated COVID-19

A retrospective cohort study was conducted on 52 patients with COVID-19 pneumonia admitted to Zhongnan Hospital of Wuhan University from 20 January to 28 February 2020. The most common initial symptoms were fever, fatigue, dry cough, myalgia, and dyspnea. Less common symptoms were headaches, dizziness, abdominal pain, diarrhea, nausea, and vomiting. Out of 52 patients, there were nine patients (17%) who presented with pancreatic injury, as defined by elevated amylase or lipase. Patients with pancreatic insult had an average age of 55 years. Other laboratory test results in this group showed a decrease in lymphocytes and an increase in hepatic and inflammatory indicators ^[1].

Another retrospective observational cohort study was conducted on patients 18 years or older admitted to 12 hospitals within the Northwell Health System from 1 March to 1 June 2020, during the COVID-19 pandemic in New York. During this period, 48,012 patients were hospitalized, and 11,883 of 48,012 (24.75%) were COVID-19 positive on admission ^[2]. The COVID-19 pneumonia cases were not described in this study. Patients were identified as presenting with acute pancreatitis on admission if they met all three of the following criteria: lipase level greater than 3 times the upper limit of normal, computed tomography or magnetic resonance imaging showing pancreatitis, and characteristic upper abdominal pain at admission ^[3]. A total of 189 of 48,012 (0.39%) met criteria

for a diagnosis of pancreatitis, and 32 of 189 (17%) were COVID-19 positive, yielding a point prevalence of (0.27%) of pancreatitis among the 11,883 patients with COVID-19 associated hospitalizations. With respect to outcomes, patients with pancreatitis who were also COVID-19 positive were more likely to require mechanical ventilation and had longer lengths of hospital stay compared to patients with pancreatitis without COVID-19 [2]. In a systematic search paper [4] citing the above retrospective study, the suggestion was made to conduct autopsies on a series of patients with COVID-19 with and without concomitant clinically evident acute pancreatitis, as it might help in revealing the mechanisms behind this possible, yet unproven, association.

A retrospective cohort study was conducted to assess the impact of COVID-19 on pancreatic injury in a US population. A total of 71 hospitalized patients across six US centers (two tertiary and four community hospitals) with COVID-19 who had lipase levels measured were included. Hyperlipasemia was defined as an elevated lipase level above the upper limit of normal (>60 U/L). Poor outcomes included intubation, intensive care unit (ICU) admission, and death. Demographic data, presenting symptoms, imaging, and laboratory data were obtained from medical records. The study did not mention if study subjects had pulmonary or other organ involvement. The mean age of all patients was 64.9 years. Thirty-nine patients (53.5%) were women, and the average body mass index of all patients was 29.5 (SD \pm 6.6). Nine patients (12.1%) had hyperlipasemia >60 U/L on admission. Gastrointestinal symptoms were common among the nine patients with hyperlipasemia, including five (55.6%) with nausea, six (66.7%) with anorexia, three (33.3%) with general abdominal discomfort, and five (55.6%) with diarrhea. None of the cases showed any features characteristic of AP on abdominal CT [5].

A retrospective analysis was conducted on patients diagnosed with COVID-19 from 1 January 2020 to 15 February 2020 in Wuhan Tongji Hospital and Wuhan Jin Yin-tan Hospital. Patients' hospital admission data, laboratory tests, and imaging tests from clinical electronic medical records were reviewed. Severe COVID-19 was defined when patients had one of the criteria such as shortness of breath and respiratory frequency ≥ 30 /min, finger pulse oximeter oxygen saturation at rest of 93% or less, or oxygenation index of 300 mm Hg or less. In this study cohort, 121 COVID-19 patients were included (46 women, 75 men). In 54 mild cases, one (1.85%) had increased levels of both amylase and lipase. In patients with severe COVID-19, 12 of 64 (17.91%) and 11 of 64 (16.41%) had increased amylase or lipase levels, respectively. In addition, some critically ill patients had already developed pancreatic injury before admission, and drug-induced pancreatitis should be considered a possibility because of the history of taking nonsteroidal anti-inflammatory drugs, glucocorticoids, and other experimental therapies in some of the cases [6].

In a multivariable-adjusted model, a cohort study was conducted at Rush University Medical Center in Chicago, Illinois, between 12 March and 3 April 2020. Of the 294 COVID-19-positive patients admitted to the hospital, 83 patients (18%) were tested for lipase, and 14 of the 83 (16.8%) had elevated lipase levels. A significant predominance of men was observed. There were 26 male patients of 69 total patients (38.8%) in the low lipase group compared with the 11 of 14 patients (78.6%) with elevated lipase group ($p = 0.009$). However, no other significant difference was observed in the demographics of the two groups except higher symptoms of nausea or vomiting reported in 52 of 69 patients (75.4%) in the low lipase group versus 6 of 14 patients (42.9%) in the high lipase group ($p < 0.025$). There was no other significant difference in recorded gastrointestinal symptoms such as

abdominal pain or diarrhea between the two groups. Moreover, the elevated lipase level in both groups was significantly associated with higher rates of admission to the ICU and intubation after adjusting other confounders such as age, sex, BMI, history of diabetes, and history of hypertension [7].

Mass General Brigham Healthcare Institutional Review Board approved a retrospective study [8] on all the adult patients older than 18 years of age who were admitted with a diagnosis of COVID-19 and AP from 1 February to 30 June 2020. Results are presented using pooled data from Massachusetts General Hospital, Brigham and Women's Hospital Brigham and Women's Faulkner Hospital, North Shore Medical Center, and Newton–Wellesley Hospital. COVID-19 disease was confirmed by detecting SARS-CoV-2 nucleic acid in throat swab by reverse-transcription PCR assay. Lipase level was tested in 985 COVID-19 patients. A further search was conducted to include patients with concurrent diagnoses of AP and COVID-19. A total of 17 patients were found eligible for the study. Out of 17, nine patients (52.9%) were primarily hospitalized for coronavirus disease-associated acute respiratory distress syndrome requiring intubation and mechanical ventilation. These patients developed AP after a median 22.5 days (range 13–76 days) from the onset of COVID-19 symptoms. The remaining eight patients (47%) presented with symptomatic AP on admission. Of eight, three (37.5%) patients developed respiratory and constitutional symptoms of COVID-19 illness, one (12.5%) before the diagnosis of AP, and two patients (25%) developed fever and cough after 3 days of hospitalization. The median peak lipase among mechanically ventilated patients was higher (661 vs. 236 U/L). One patient in each group did have elevated lipase, but their clinical course and CT imaging were characteristic of AP. In the first cohort of nine patients, five (55.6%) underwent CT imaging of the abdomen. Typical findings of AP were appreciated in three (33.3%) patients while the pancreas was reported normal in other two patients (22.2%). Necrotizing pancreatitis was present in one patient (11.1%). Among the remaining four of nine patients (44.4%), CT was not performed due to hemodynamic instability in three patients (33.3%), and the fourth patient (11.1%) developed AP with typical symptoms. In the second cohort of eight patients, seven (87.5%) underwent CT. Five patients (62.5%) had typical radiological finding of AP; however, the pancreas was read as normal in the remaining two patients (25%).

Moreover, a retrospective study was conducted involving 42 COVID-19 patients who were diagnosed using real-time PCR and were admitted to a tertiary care hospital in New Delhi. Serum amylase and serum lipase levels were measured. Serum amylase was elevated in 14 of the 42 patients (33%). Serum lipase was elevated in 7 out of 29 patients (24.1%). Mortality was seen in 18 patients (42.8%). Serum amylase or lipase did not correlate with severity of COVID-19 or its mortality. Although the prevalence of hyperamylasemia and elevated amylase in patients of COVID-19 were 33% and 24.1%, pancreatic injury is not statistically significant in relation to the severity or outcome of COVID-19 [9].

A prospective observational single center study was conducted in the respiratory unit at San Paolo Hospital in Milan, Italy from 1 April to 30 April 2020 [10]. One hundred and ten consecutive patients met the inclusion criteria of the study to be at an age equal to or greater than 18 years, both genders included, recent coronavirus infection confirmed by real-time polymerase chain reaction, and clinically diagnosed with COVID-19 per WHO guidelines. This, in addition to chest CT scans, confirmed lung compromise. None of the patients complained of abdominal pain. Of the 110 patients, 14 (12.7%) had diarrhea and 3 (2.7%) had nausea/vomiting. There was only one patient

who experienced all three symptoms. None of the patients studied developed clinical signs consistent with acute pancreatitis. The serum levels of amylase, lipase, total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, γ -glutamyl transpeptidase, and C-reactive protein were recorded during the patients' initial observation. Results showed 27 of 110 patients (24.5%) had amylase values above 53 IU/L and 18 patients of 110 (16.4%) had lipase values above 300 IU/L. Only one patient of the included patients (0.9%) had values of both amylase and lipase more than 3x the upper normal limit. There was also no statistically significant difference in amylase and lipase serum activities in patients who complained of GI symptoms and in those who did not.

From a different perspective, studies have been conducted to assess contributing risk factors for AP associated COVID-19 and disease outcome. In a cohort study of 35 patients evaluated at the Royal Liverpool University Hospital between 14 March and 30 April 2020, registered with the Liverpool University Hospitals NHS, cases were identified by searching admission diagnoses or radiology requests and reports for AP. In data extracted from patient and radiology records of contrast-enhanced computed tomography (CECT) images, as reported by an expert pancreatic radiologist, 25 of 35 patients who presented with acute pancreatitis were negative for SARS-CoV-2 and were excluded. Of the 10 patients who tested positive for SARS-CoV-2, a further five were excluded because they presented with a clearly defined etiology of AP (such as choledocholithiasis) with confirmed AP. The five remaining patients were young adult males with a median age of 42 years, overweight or obese with evidence of metabolic distress. Serum amylase was elevated with abdominal CT to confirm the diagnosis, but importantly they had no prior pancreas symptoms. This study postulated that the combination of male sex, abdominal pain, metabolic stress, and CT findings of remarkable for pancreatic inflammation reflects AP in patients infected with SARS-CoV2. Additionally, patients with pre-existing metabolic syndrome can be predisposed to AP considering the high body mass indices as in this study [\[11\]](#). The small number of subjects render these conclusions interesting and worthy of further study.

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