

Acute Pancreatitis Associated with Severe COVID-19: A Cross-Sectional Study

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ABSTRACT

Background: There is a growing body of evidence suggesting that the pancreas is an organ targeted by the SARS-CoV-2 virus. Acute pancreatitis has been demonstrated to be a presenting feature of COVID-19 in observational studies and case series. However, none of those studies examined the correlation between COVID-19 severity and acute pancreatitis.

Purpose: This study investigates the association between acute pancreatitis and severe cases of COVID-19.

Methods: This cross-sectional study recruited COVID-19 patients who presented with acute pancreatitis. COVID-19 was confirmed via a PCR test or a CT scan of the chest or abdomen. Abdominal CT scans and pancreatic enzymes were used to diagnose acute pancreatitis. The severity of COVID-19 was assessed and classified according to the National Institutes of Health classification. ANOVA was used to test the association between acute pancreatitis and COVID-19 severity.

Results: Thirty-two COVID-19 patients with acute pancreatitis enrolled in this study. The mean age of the participants was 57.6 ± 12.5 years. The patients' mean serum pancreatic enzyme level was 419.5 ± 160.6 U/L and 290 ± 114 U/L for lipase and amylase, respectively. There was a significant positive correlation between the level of pancreatic enzymes and COVID-19 severity, ferritin level and C-reactive protein.

Conclusions: Acute pancreatitis is associated with severe COVID-19. Higher levels of pancreatic enzymes were reported among more severe COVID-19 cases.

Key words: COVID-19, acute pancreatitis, lipase, amylase, ferritin

INTRODUCTION

Coronaviruses are a group of related RNA viruses that cause diseases in mammals and birds. Over the last 20 years, several viral epidemic diseases have emerged that represent a serious issue for public health [e.g., severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, H1N1 influenza in 2009, and most recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (1)].

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On 3 December 2019, unexplained lower respiratory tract infections were detected in Wuhan, China and first reported to the World Health Organization (WHO) Country Office in China as "pneumonia of unknown etiology" (1). The Chinese Center for Disease Control and Prevention (CDC) and local CDCs organized an intensive outbreak investigation. The etiology of this disease was attributed to a novel virus belonging to the coronavirus (CoV) family called severe acute respiratory syndrome coronavirus 2 ("SARS-CoV-2") (2).

Patient with COVID-19 may present with mild, moderate, or severe illness. Severe clinical manifestations include severe pneumonia, acute respiratory distress syndrome, as well as extra-pulmonary manifestations and systemic complications such as sepsis and septic shock (1).

Patients typically present with fever and respiratory symptoms; nevertheless, some patients have gastrointestinal manifestations such as diarrhea, vomiting and abdominal pain (2).

There are abundant viral receptor expressions on gastrointestinal epithelial cells, and recent studies have suggested possible fecal-oral transmission of COVID-19 (3). It has been suggested that preventive measures against fecal contamination should be implemented given the prolonged duration of viral shedding in stool (i.e., up to 16 days from the onset of symptoms) (3).

Acute pancreatitis is one of the most important gastrointestinal causes of hospital admission worldwide (3). Its most common causes include cholelithiasis, excessive alcohol intake and viral infection (3). Recent data have suggested that the pancreas is a target for the SARS-CoV-2 virus due to the presence of ACE2 receptors on the acinar and islet cells of the pancreas, which allow the virus to invade cells (4). The severity of COVID-19 can be classified according to the criteria listed in *table 1* (5,6).

Acute pancreatitis is typically a mild illness and resolves spontaneously without serious complications in 80% of cases (5). Its etiology and pathogenesis have been extensively investigated worldwide for centuries (7). The etiology of acute pancreatitis is variable and includes viral, bacterial and parasitic infections (8).

The islet cells of the pancreas contain ACE2 receptor proteins to which SARS-CoV-2 can bind and cause pancreatic injury (7). A large retrospective observational cohort study conducted in the United States reported a point prevalence rate of acute pancreatitis of 0.39% for patients hospitalized with COVID-19 (7). Several case reports and observational studies have demonstrated that acute pancreatitis is an initial presentation of patients with COVID-19 (2-4). However, none of those

Table 1 - Classification of severity of COVID-19 according to clinical criteria

Classification	Clinical criteria
Mild	Mild clinical symptoms [fever <38°C (quelled without treatment), with or without cough, no dyspnea, no gasping, no chronic disease. No imaging findings of pneumonia]
Moderate	Fever, respiratory symptoms, imaging findings of pneumonia
Severe	Meet any of the followings: Respiratory distress RR 23 times/min SpO2 <93% at rest PaO2/FiO2 <300 mmHg Patients showing a rapid progression (>50%) on CT imaging within 24–48 hours
Critical	Meet any of the followings: Respiratory failure need mechanical assistance Shock "Extra pulmonary" organ failure intensive care unit needed

FiO2: fraction of inspired oxygen, PaO2: partial pressure of oxygen, RR: respiratory rate, SpO2: oxygen saturation.

reports examined the association between acute pancreatitis and COVID-19 severity. We therefore investigated the association between acute pancreatitis and the severity of COVID-19.

MATERIAL AND METHOD

Study design and population

This prospective study was conducted from June 2020 through November 2021. A total of 60 patients were enrolled from Al-Sadir Teaching Hospital in Basrah City, Iraq. The patients included in this study had been diagnosed with COVID-19 using real-time reverse-transcription polymerase chain reaction (RT-PCR) or computed tomography (CT) scans of the chest and abdomen; they had no risk factors for acute pancreatitis. All of the patients were aged 18 or older. Patients were classified into mild, moderate, severe and critical cases of COVID-19 as per clinical criteria (*table 1*). Patients were identified as presenting with acute pancreatitis upon admission if they satisfied all of the following criteria: 1) a lipase level greater than three times the upper limit of normal, 2) cross-sectional (CT) imaging showing pancreatitis and 3) characteristic upper abdominal pain upon admission (6). Twenty-eight patients were excluded because they satisfied one or more of the exclusionary criteria listed below:

1. Autoimmune diseases.
2. Heavy alcohol consumption.
3. Gallstones.
4. On medications known to cause pancreatitis.

5. Metabolic disorders.
6. Recent surgery.
7. Recent trauma to the abdomen.
8. Hypertriglyceridemia.
9. Hypotension (patients unwell to complete or enrolled in this study).
10. Critical patient with COVID-19 (uncomfortable patients for enrolling in this study due to critically illness).

Ethics and consent

Informed consent was obtained from all patients, and their identities remained anonymous during the entire study process. This study was ethically approved by the Scientific Committee of the Department of Internal Medicine and the Ethical Committee of College of Medicine, University of Basrah. All methods were carried out in accordance with guidelines and regulations followed at the College of Medicine and its Teaching Hospital (AL-Sadder Teaching Hospital). The research was conducted according to the good clinical practice guideline, as well as the Declaration of Helsinki.

Clinical evaluation and anthropometric measurements

The patients were classified according to the National Institutes of Health (NIH) classification for severity of COVID-19 into mild, moderate and severe cases (6). Blood samples were collected for serum amylase, serum lipase, C-reactive protein (CRP) and serum ferritin and measured using an automated biochemical instrument (SPIN 200 E, SPINREACT, City, Spain).

Statistics

The data were statistically analyzed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). The association between the severity of COVID-19 and acute pancreatitis was analyzed using an ANOVA test given that the data

were categorical, ordinal and parametric. Logistical regression analysis of univariate and multivariate models of severity was applied using an odds ratio (OR). A P value of less than 0.05 was presumed to indicate statistical significance.

RESULTS

Thirty-two people satisfied the inclusionary criteria. The mean age of the participants was 57.6 ± 12.5 years (range: 32–82 years). The sample was 65.6% male patients and 34.4% female patients. The patients' mean serum amylase and lipase levels were 298.4 ± 113.8 U/L and 419.5 ± 160.6 U/L, respectively.

Pancreatic enzyme levels were higher in the female patients than in the male patients. However, the difference was not statistically significant ($P=0.06$). There was a statistically significantly higher level of serum lipase in patients who coughed ($P=0.02$). However, no statistically significant differences were observed in pancreatic enzyme levels when the patients were sorted according to other symptoms such as dyspnea ($P=0.78$), fever ($P=0.99$), backache ($P=0.1X$), sneezing ($P=0.75$), flu-like illnesses ($P=0.66$), sore throat ($P=0.08$), chest pain ($P=0.09$), nausea ($P=0.06$), vomiting ($P=0.92$) and abdominal pain ($P=0.08$). There was a strong and significant positive correlation between serum ferritin and CRP with pancreatic enzymes level (lipase: $r= 0.594$, $P<0.001$; $r= 0.585$, $P<0.001$. amylase: $r= 0.58$, $P=0.001$; $r= 0.582$, $P<0.001$).

Interestingly, we found a significant positive correlation between COVID-19 disease severity and pancreatic enzyme level (*table 2*).

Data from the logistic regression analysis of the univariate and multivariate models of the severity are listed in *table 3*. Lipase, amylase, ferritin and cough were statistically significant predictors of the severity of COVID-19.

DISCUSSION

COVID-19 infections primarily affect the respiratory

Pancreatic enzyme	COVID19 severity			P value
	Mild (n=13)	Moderate (n=12)	Severe (n=7)	
Serum lipase Mean \pm SD U/L (95%CI)	324.7 \pm 64.2 (285.9-363.6)	409.6 \pm 148.3 (315.4-503.8)	612.2 \pm 147.2 (476.0-748.4)	<0.0001
Serum amylase Mean \pm SD U/L (95%CI)	242.5 \pm 82.3 (192.7-292.3)	288.0 \pm 92.4 (229.2-346.7)	420.0 \pm 116.1 (312.6-527.3)	<0.0001

Table 2 - Association between the severity of COVID 19 and pancreatic enzymes

Table 3 - Logistic regression analysis of univariate and multivariate models of the severity

Parameter	Univariate (OR)	P value (OR)	Multivariate	P value
Age	1	0.07	-	-
Sex	1	0.99	-	-
Lipase	0.6	<0.0001	0.95	<0.0001
Amylase	0.75	<0.0001	0.96	<0.0001
Ferritin	1.55	<0.0001	0.89	0.001
CRP	1.75	0.001	1	0.65
Cough	1.25	0.02	0.98	0.01
Dyspnea	1	0.78	-	-
Fever	1	0.99	-	-
Backache	1	0.1	-	-
Sneezing	1	0.75	-	-
Sorethroat	1	0.08	-	-
Flu-like illness	1	0.66	-	-
Chest pain	1	0.09	-	-
Nausea	1	0.06	-	-
Vomiting	1	0.92	-	-
Abdominal pain	1	0.08	-	-

system (8). However, the effects of COVID-19 on the gastrointestinal and pancreatic-biliary systems have become increasingly obvious (8,9). Abdominal pain is most prevalent in people who have a severe illness (10,11). Furthermore, viral RNA has been detected in the fecal samples and gastrointestinal epithelium of patients who have COVID-19-negative respiratory tests (10). All of the results noted above support the fecal-oral transmission of COVID-19 (4,10).

We noted elevated pancreatic enzymes in all 32 patients who complained of gastrointestinal symptoms such as severe abdominal pain, nausea, and vomiting. That finding is consistent with other studies (10,11). Higher levels of pancreatic enzymes were also noted in females than males; however, that difference was not statistically significant. This result was also reported by another study (12).

We found a positive significant correlation between pancreatic enzyme levels and COVID-19 severity: higher enzyme levels were correlated with more severe cases that often required hospital admission. These findings are in line with those of other studies (11,12). Dirweesh et al. (12) noted a complex interaction between acute pancreatitis and COVID-19 that places the patients at high morbidity and mortality risk has been found. However, those authors were unable to determine the nature of that interaction. According to our findings, pancreatitis is associated with severe COVID-19 cases that necessitate hospitalization and occasional

ventilator support, which is in agreement with other studies (13-15).

Interestingly, another large, prospective, international, multicenter cohort study reported a high 30-day mortality rate among patients with acute pancreatitis and COVID-19, where the latter was linked to the severity of pancreatitis (14).

Another prospective study conducted in Germany found high serum lipase levels without typical signs of pancreatitis in patients with severe COVID-19 presenting with XXX (ARDS) (13). Acute pancreatitis was confirmed in all of our cases clinically, radiologically with a CT scan of the abdomen and biochemically by lipasemia. Similarly, a retrospective study conducted in Thailand concluded that gastrointestinal manifestations of COVID-19 are common symptoms that are typically associated with severe COVID-19 cases (15). However, that investigation focused on gastrointestinal tract symptoms in general rather than acute pancreatitis as an entity.

A possible explanation for this association is that infections with the SARS-CoV-2 virus can lead to increased expression of ACE2 receptors on the pancreatic islet cells. That situation in turn results in injury to the endocrine and exocrine pancreatic cells. The end result is acute pancreatitis and hyperglycemia (4). Another possibility is that the intense inflammatory response induced by the viral infection is reflected in extremely high inflammatory markers that result in damage to multiple organs, including the pancreas. Such an exaggerated inflammatory reaction has been associated with increased morbidity and mortality (16).

In our study, ferritin and CRP levels were found to be significantly correlated with pancreatic enzyme levels. Both ferritin and CRP are inflammatory markers and might serve as surrogate markers of the degree of pancreatic inflammation. This finding has not been noted in previous studies.

Common symptoms of COVID-19 (e.g., fever, cough, dyspnea, abdominal discomfort and vomiting) were all linked to pancreatic enzymes levels. However, cough was the only symptom that was statistically significantly correlated in a positive way with pancreatic enzyme levels.

The limitations of our study include its small sample size and lack of comparison with other factors that may affect disease severity (e.g., obesity, vaccination status, age and other commodities). Furthermore, clinical outcomes of the studied patients were not reported. On the other hand, our study benefits from strict criteria used to diagnose acute pancreatitis and determine COVID-19 severity. This study is the first, to the best of our knowledge, to demonstrate a statistically significant

correlation between acute pancreatitis and severe COVID-19 cases.

CONCLUSIONS

Acute pancreatitis can possibly be used as a predictor of COVID-19 severity. Higher levels of pancreatic enzymes in patients with COVID-19 complicated by acute pancreatitis can reflect COVID-19 disease severity. Pancreatic enzymes should be measured in patients with COVID-19 who present with abdominal pain to exclude acute pancreatitis as a complication, particularly in severe cases. Additional large prospective cohort studies are necessary to confirm our findings.

Author's contributions

F. Al-khaqani; Conceptualization; Methodology; Investigation; Resources; Data Curation; Writing - Original Draft. A. G. Fadil; Conceptualization; Methodology; Data Curation; Writing - Original Draft, soft wire. R. M. Al-amiri; Conceptualization; Investigation; Resources; Writing - Original Draft, soft wire. M. Alabbod; Conceptualization; Methodology; Resources; Data Curation; Writing - Original Draft, soft wire.

Competing interests

The authors declare that they have no competing interests.

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