COVID-19 and acute biliary pancreatitis: comparative analysis between the normal period and COVID-19 pandemic

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Serhat Meric, Talar Vartanoglu Aktokmakyan, Merve Tokocin, Yunus Emre Aktimur, Nadir Adnan Hacim, Erkan Yavuz

General Surgery Department, Istanbul Bagcilar Training and Research Hospital, Istanbul, Turkey

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BACKGROUND: *The development of acute pancreatitis is multifactorial requiring predisposition and relevant injury.Viral acute pancreatitis has been described in other viral infections.However, pancreatic involvement in SARS-CoV-2 infection is still poorly defined.The present comparative study reports the patients with acute pancreatitis during the COVID-19 pandemic and last year covering the same period to appraise the link between COVID-19 and acute biliary pancreatitis.*
METHODS: *The retrospective observational study was conducted in acute biliary pancreatitis patients from 13.03.19to13.09.19 and from 13.03.20to13.09.20 respectively.*
RESULTS: *The study included 181patients(105patients in 2019;76 patients in 2020(during COVID-19 pandemic)).The patients were named as Group A(Normal period)and GroupB(Pandemic period),respectively.The groups were found to be comparable as there was no significant difference between the mean age, sex, comorbidities, cholecystectomized, and recurrency.There is no significant difference in the laboratory and radiological findings of GroupA and GroupB.*
However, there is a significant difference between the COVID-19 positive and negative patients in GroupB in terms of Glucose levels(p=0,025)and the presence of edema or necrosis in radiological images(p=0,046).There is a significant difference between the patients' number with abdominal pain of acute biliary pancreatitis in 2019and2020.(p=0)The length of stay was statistically significant in COVID-19 positive patients.(p= 0,013)
CONCLUSIONS: *Clinicians involved in the management of acute pancreatitis should be aware of its existence in the context of COVID-19.Understanding of the disease process and clinical manifestations of COVID-19 is still developing.Awareness of these issues and addressing them adequately will be crucial for the management.*

KEY WORDS: Acute Biliary Pancreatitis, Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Introduction

Pneumonia caused by SARS-CoV-2 infection emerged in Wuhan City, China in December 2019. The novel coronavirus disease-19 (COVID-19) has reached above 79,461,042 confirmed cases worldwide [1]. Although the most common symptoms include cough, shortness of breath and fever, gastrointestinal manifestations of COVID-19 are progressively being recognized. The development of acute pancreatitis is multifactorial requiring predisposition and relevant injury [2]. The most common causes of acute pancreatitis are gallstones and alcohol abuse, but viral-induced acute pancreatitis has also been described [3]. Acute pancreatitis is a common disease, being the gastrointestinal disease most frequently requiring acute hospitalization [4]. Viral acute pancreatitis has been described in other viral infections. However, pancreatic involvement in SARS-CoV-2 infection is still poorly defined.The association between COVID-19 and pancreatitis has been limited to a few case reports, mostly in adult patients. Herein, the present comparative study reportsthe patients with acute pancreatitis during the COVID-19 pandemic and last year covering the same period to appraise the link between COVID-19 and acute biliary pancreatitis.

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Corresponence to: Talar Vartanoglu Aktokmakyan, Merkez Mah, Istanbul Bagcilar Training and Research Hospital, Bagcilar, Istanbul (e-mail: talarim@gmail.com)

Material and Methods

Data were collected from patients admitted with COVID-19 between March-September 2020 (pandemic period) and the same period in March-September 2019 to the General Surgery Department of Istanbul Bagcilar Training and Research Hospital retrospectively. Acute pancreatitis was diagnosed according to the Ranson classification. Throat swab samples and tracheal aspirates were collected from all patients and SARS-CoV-2 was detected using real-time transcription-polymerase chain reaction (RT-PCR) assay. Blood samples and diagnostic imaging were performed according to clinical practice. This study was reviewed and approved by the local data and ethics committee (2020.10.2.02.163) and the Ministry of Health.That is, acute pancreatitis corresponding to the pandemic process were compared with acute pancreatitis performed in the same period last year.They were classified according to the year of stay in the hospital for medical care as Group A and Group B.An evaluation was made of characteristics of patients, comorbidities, RT-PCR tests, laboratory findings, radiological findings, clinical findings, length of stay, complications, need for Intensive Care Unit, and mortalities. The data was collected using Microsoft Excel®, and the variables were analyzed using the IBM SPSS Statistics® 25.0 statistical packages. Chi-square test and Mann-Whitney *U* test were used for statistical analysis."p-value" less than 0.05 was considered statistically significant ($p<0.05$).

Table I - *Characteristics of 2019 and 2020 patients with acute pancreatitis*

Acute pancreatitis	Group A (n=105)	Group B (n=76)	p
Mean Age	57,31±18,05	56,84±21,5	0,83
Female/Male	67/38	47/29	0,98
Comorbidities	53	41	0,645
Cholecystectomized	17	16	0,403
Recurrency	54	50	0,54

Table II - *Laboratory findings of included patients*

Laboratory Findings	Mean of Group A	Mean of Group B	p
White- Cell Count (10x3/uL)	10,8±4,1	11,3±4,2	0,41
C-Reactive Protein (mg/L)	40,31±76,07	58,02±103,74	0,871
Amylase (U/L)	1523±1380	1816±1507	0,098
Lypase (U/L)	3249±3245	3677±3015	0,151
International Normalized Ratio	1,13±0,023	1,13±0,19	0,411
Glucose (mg/dL)	140±42	145±71	0,45
			0,025*
Lactate Dehydrogenase (U/L)	437,14±257,25	442,75±214,72	0,664
Aspartate Aminotransferase (U/L)	261±243	254±225	0,967
Creatinine (µmol/L)	0,79±0,4	0,89±0,74	0,403

Results

The study included 181 patients (105 patients in 2019; 76 patients in 2020 (during COVID-19 pandemic) with a mean age of 57,3 and 56,8 respectively. (Table I) The patients were named Group A (Normal period) and Group B (Pandemic period), respectively, according to the year, they were hospitalized. The groups were found to be comparable as there was no significant difference between the mean age, sex, comorbidities, cholecystectomized, and recurrency.

According to the laboratory and radiological findings, patients were categorized (Table II, III). There is no significant difference in the laboratory findings of Group A and Group B. However, there is a significant difference between the COVID-19 positive and negative patients in Group B in terms of Glucose levels. (p=0,025)* Moreover, there is no significant difference in both ultrasonography and computerized tomography findings of Group A and B. However, when the presence of edema or necrosis was examined in radiological images, a statistically significant difference was observed between the two groups. (p=0,046)

When the patients were evaluated according to the Ranson criteria, no statistically significant difference was observed between group A and group B in terms of Ranson values calculated at the time of admission and Ranson values at the 48th hour. (p=0,459 and p=0,615) According to the clinical findings, patients were categorized in Table IV. According to the RT-PCR (Reverse transcription-polymerase chain reaction) test and/or radiological scanning of the lung, there were 13 COVID-19 positive and/or suspicious patients in Group B. There is a significant difference between the patients' number with abdominal pain of acute pancreatitis in 2019 and 2020. (p=0) Moreover, The length of stay was statistically significant in patients with COVID-19 PCR posi-

Table III - *Radiological findings of included patients*

Radiological Findings	Group A	Group B	p
US(+)	99	71	0,81
CT(+)	13	18	0,046

(US: Ultrasonography, CT: Computerized Tomography)

Table IV - *Clinical findings of included patients*

Clinical findings	Group A	Group B	p
Abdominal pain	104	62	0
Length of stay	3,84	4,45	0,013
ICU need	5	7	0,235
Complication	22	15	0,841
Mortality	2	5	0,107

tive and/or CT positive. (p= 0,013) There is no significant difference between theneed for intensive care unit(ICU), complication, and mortality of acute pancreatitis in 2019 and 2020.

Discussion

The novel coronavirus disease 2019 (COVID-19) began in Wuhan, China, at the end of 2019 and spread rapidly worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections primarily influence the respiratory tract, however, gastrointestinal manifestations such as nausea, vomiting, and diarrhea also occur clinically. The development of acute pancreatitis is multifactorial requiring predisposition and relevant injury to the organ. Recent studies have reported acute inflammation in the pancreas due to HIV, Cytomegalovirus, Coxsackievirus B, and Influenza A (H1N1); however, the incidence of viral acute pancreatitis is unknown [5].

According to the available guidelines, the diagnosis of acute pancreatitis requires at least two of the three following signs, abdominal pain, amylase or lipase three times the upper normal limit, and characteristic findings on diagnostic imaging [6]. In our study, when the decrease in the number of patients with abdominal pain is examined; we think that the emergency administrations are decreasing, primarily because of the curfew of people and most importantly because they are afraid of pandemics. In this study, we reveal that the patients who apply, wait until the last moment and apply when they cannot tolerate suffering.

Therefore, we think that we are confronted with a clinical picture of advanced pancreatitis accompanied by necrosis and edema.Last studies have verified that COVID-19 may be associated with gastrointestinal symptoms including abdominal pain and have identified viral RNA in the gastrointestinal tract [7]. Wang et al. reported at admission 17% of 52 patients with COVID-19 had slightly abnormal amylase or lipase [8]. Liu et al showed an increase in amylase and lipase in a series of 121 patients admitted with COVID-19 pneumonia, suggesting some degree of pancreatic injury in these patients [9].

However, no information about the clinical picture was given since patients were stratified based on the severity of the respiratory disease. Several elements may participate in the development of acute pancreatitis with the inclusion of pancreatic autodigestion, enzyme activation, complement system activation, microcirculation disturbance theory, leukocyte excessive activation, and pancreatic acinar cell apoptosis and necrosis. Viral pancreatitis proceeds due to the direct destroying of pancreatic acinar cells by inflammation and edema. Injury to the pancreatic acinar cells by the virus could lead to a leaking intracellular enzyme or precipitates a process of cell death.

The entry receptor Angiotensin-converting enzyme 2 (ACE2) for SARS-CoV-2 has been identified in the gastrointestinal epithelium of infected cases. During the 2002–2004 pandemic, SARS-CoV used ACE2 for entry to host cells. Increased expression in pancreatic islets was observed which leads to acute diabetes in the end [10]. Gene sequences of SARS-CoV have demonstrated that 79.6% are shared with SARS-CoV-2 [11].

The expression of ACE2 in the pancreas during SARS-CoV-2 infection could therefore lead to acute inflammation like acute pancreatitis. So, an elevated serum amylase level in patients presenting with COVID-19 should not be directly attributed to pancreatitis without appropriate imaging to support the diagnosis. At the same time, the same hypothesis explains the significant difference in glucose between covid-positive and negative patients.

Of course, we will never understand comprehensibly whether acute biliary pancreatitis we encountered in the clinic during the pandemic developed secondary to COVID-19 or whether COVID-19 was added to pancreatitis. While there was no direct evidence of viral pancreatitis in our case, the temporal relationship between pancreatitis and COVID-19, and lack of other etiologies would suggest coronavirus-induced pancreatitis. Further studies are needed to establish the real prevalence and clinical significance of pancreatic injury in COVID-19 patients.

Coronavirus disease 2019 (COVID-19) can be a new etiology for acute pancreatitis. If so, acute pancreatitis can complicate the course of COVID-19. In case of this association, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause acute pancreatitis without causing typical COVID-19 disease with respiratory symptoms, and patients may present with idiopathic acute pancreatitis and can be recognized as SARS-CoV-2 positive only by a screening swab.In a cohort study of 412 patients with COVID-19, up to 54% undergoing ultrasound imaging (mostly for abnormal liver enzymes) were found to have gallbladder distention and sludge [12]. Abnormal abdominal imaging is common among patients with COVID-19 [13]. However, the significance of those findings is unclear.

Essential imaging, especially contrast-enhanced CT abdomen can be vital in patients with COVID-19 with abdominal pain especially for the detection of pancreatic edema and necrosis.

Consequently, the adoption of a low threshold for escalation to the intensive care unit is vital in patients presenting with acute biliary pancreatitis and COVID-19. In our study, covid-positive patients in PCR test and/or tomography were found to be prolonged in-hospital stay, and this was thought to be due to additional medical treatment for COVID-19 treatment.

As it was noticed in our study, late admission of patients due to pandemic fear and street restrictions causes patients to admit to the hospital with advanced tomog-

raphy findings and regression of symptoms such as abdominal pain.
Of course, our study was carried out retrospectively with a small sample under pandemic conditions, and since Covid-19 is a new entity, larger studies are needed.

Conclusions

Clinical data on COVID-19 with pancreatic injury is very limited. Clinicians involved in the management of acute pancreatitis should be aware of its existence in the context of COVID-19. Only with global collaborative research networks that expand as rapidly as the pandemic, will we be able to estimate the importance of this clinical phenomenon and how best to treat it. Understanding of the disease process and clinical manifestations of COVID-19 is still developing. Awareness of these issues and addressing them adequately will be crucial for the management.

Riassunto

Lo sviluppo della pancreatite acuta è multifattoriale e prevede predisposizione e danni rilevanti. La pancreatite acuta virale è stata descritta in concomitanza di altre infezioni virali. Tuttavia il coinvolgimento del pancreas nell'infezione da SARS-CoV-2 è ancora poco definita. Il presente studio comparativo riporta i pazienti con pancreatite acuta durante la pandemia di COVID-19 e durante lo scorso anno coprendo lo stesso periodo, per valutare il legame tra COVID-19 e pancreatite biliare acuta.
Lo studio, osservazionale e retrospettivo, è stato condotto in pazienti con pancreatite biliare acuta rispettivamente dal 13.03.19 al 13.09.19 e dal 13.03.20 al 13.09.20, includendo 181 pazienti (105 pazienti nel 2019; 76 pazienti nel 2020 (durante la pandemia di COVID-19).
Risultati: I 181 pazienti sono stati suddivisi rispettivamente come Gruppo A (periodo normale) e Gruppo B (periodo pandemico). I gruppi sono risultati comparabili in quanto non c'era alcuna differenza significativa tra età media, sesso, comorbidità, colecistectomia e recidiva. Non c'è differenza significativa nei risultati di laboratorio e radiologici del Gruppo A e del Gruppo B.
Tuttavia, c'è una differenza significativa tra il COVID-19 positivo e negativo nei pazienti del Gruppo B in termini di livelli di glucosio (p = 0,025) e presenza di edema o necrosi nelle immagini radiologiche (p = 0,046).
C'è una differenza significativa tra il numero di pazienti con dolore addominale di pancreatite biliare acuta nel 2019 e nel 2020. (p = 0) La durata della degenza era statisticamente significativa nei pazienti positivi al COVID-19 (p = 0,013)
Conclusioni: I medici coinvolti nella gestione della pancreatite acuta dovrebbero essere consapevoli della sua esistenza nel contesto di COVID-19. La comprensione del processo della malattia e delle manifestazioni cliniche di COVID-19 è ancora in via di sviluppo. La consapevolezza di questi problemi e affrontarli adeguatamente sarà cruciale per il trattamento.

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