

Does COVID-19 cause pancreatitis?

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ABSTRACT – Background – Viral infections can cause acute pancreatitis. Idiopathic pancreatitis has an important proportion in the etiology of acute pancreatitis. **Objective** – To investigate the rate of development of acute pancreatitis (AP) in COVID-19 patients and to determine the rate of idiopathic pancreatitis in the etiology of this pancreatitis. **Methods** – A total of 6.467 patients hospitalized with the COVID-19 diagnosis were included in the study. Patients diagnosed with AP based on the Atlanta criteria were identified. Etiological factors were determined in patients who developed acute pancreatitis and compared with the etiological factors in 315 patients with non-COVID-19, hospitalized with the diagnosis of AP before the COVID-19 pandemic. AP was detected in 0.1% of patients with COVID-19. While gallstone was the etiologic factor in 2 (28.6%) of seven patients who developed acute pancreatitis during COVID-19, hyperlipidemia was the factor for 1 (14.3%) patient. Moreover, the etiologic factor could not be determined in 4 (57.1%) patients, and they were regarded as idiopathic pancreatitis patients. Biliary pancreatitis was the most common etiologic factor in 315 (78.4%) patients admitted to the hospital for AP before the COVID-19 pandemic. Idiopathic pancreatitis was ranked second with 16.8%. **Conclusion** – It was observed that there was a significant difference in the incidence of idiopathic pancreatitis between patients with COVID-19 and non-COVID-19 ($P=0.015$). Results suggest that the SARS-Cov-2 virus may be among the factors leading to AP.

Keywords – COVID-19; acute pancreatitis; acute pancreatitis incidence; etiology.

INTRODUCTION

Coronavirus disease (COVID-19) is a viral infection that mainly affects the upper respiratory tract and lungs. It is known that this virus enters cells by attaching to angiotensin-converting enzyme two (ACE-2) receptors⁽¹⁾. The ACE-2 receptor is found not only in the respiratory system but also in many organs and tissues, mainly in the liver, biliary tract, intestine, and pancreas⁽²⁾.

Acute pancreatitis (AP) is a necroinflammatory disease of the pancreas. Many factors play a role in the etiology, while some consist of viral causes (such as mumps). Regarding the majority of acute pancreatitis cases, the underlying factors are unidentified. Idiopathic pancreatitis is defined as acute pancreatitis cases whose etiology is unclear despite detailed history, physical examination, biochemical tests, and screening methods such as abdominal ultrasonography/computed tomography. Idiopathic pancreatitis accounts for 8–44% of all pancreatitis cases^(3,4).

Although the virus was isolated in pancreatic tissue in the autopsies of people who died due to SARS-Cov infection, acute pancreatitis was not reported in these patients⁽⁵⁾. First acute pancreatitis cases were reported in COVID-19 patients in China, then similar cases were reported from other parts of the world⁽⁶⁾. Nonetheless, due to the absence of a clear definition of pancreatitis and limited retrospective studies, also the lack of emphasis on Atlanta criteria, it was not possible to present a straightforward conclusion.

Therefore, this study aims to determine the frequency of AP in patients with COVID-19 and to investigate whether COVID-19 causes AP.

METHODS

The data consists of 6467 patients admitted to Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital between April 2020 and January 2021 due to COVID-19 was analyzed retrospectively. Followingly, the data of seven COVID-19 patients diagnosed with AP were selected and scrutinized further. The etiological factors in patients with AP and COVID-19 were compared with the etiological factors in 315 acute pancreatitis patients followed up in our hospital between May 2016 and November 2019 prior to the COVID-19 outbreak. Finally, the incidence of idiopathic pancreatitis was compared across the patients with acute pancreatitis with and without COVID-19.

Patients were diagnosed with acute pancreatitis according to the revised Atlanta criteria. Therefore, patients were diagnosed with acute pancreatitis if at least two of following the criteria; 1- abdominal pain consistent with AP; (displaying posteriorly in the right upper quadrant and epigastric region); 2- amylase or lipase level increased more than three times the upper limit of average level; 3- AP-specific imaging findings (with ultrasound, computed tomography or magnetic resonance imaging) were present⁽⁷⁾.

A group of patients was excluded from the study; for instance, patients with a diagnosis of chronic pancreatitis, with a diagnosis of hereditary pancreatitis, previous pancreatic or biliary tract surgery, patients with pancreatic and other organ malignancies, patients with sepsis, septic shock, and multiorgan dysfunction.

The study was carried out per the declaration of Helsinki, and

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permission for the study was obtained from the Health Sciences University Diyarbakir Gazi Yasargil Training and Research Hospital Ethics Committee. (Date 16.10.2020 and issue number 611).

Statistical analysis

While mean and standard deviation values were stated for continuous variables, categorical variables were expressed as %. Student's *t*-test and Mann Whitney U test were used to compare the factors between patients who developed pancreatitis during non-COVID-19 and COVID-19 infection. All tests were bilateral, and a *P*-value <0.05 was considered statistically significant. Statistical analyzes were performed using the SPSS26.0 for Windows (SPSS Inc.Chicago, IL, USA) package program.

RESULTS

Acute pancreatitis developed during hospitalization in 7 (0.1%) of 6467 patients with COVID-19. Of these patients, three were female, and four were male, with a mean age of 51.4. One of the patients had diabetes, and one had hypertension. Of 315 patients without COVID-19 were hospitalized for acute pancreatitis, 212 (67.3%) were female, and 103 (32.7%) were male. 4 (1.2%) of these patients hospitalized due to acute pancreatitis died. Of all the patients, at least one comorbid disease was present in 116 (36.8%), and the most common ones were hypertension, diabetes, and coronary artery disease (TABLE 1).

Biliary pancreatitis was the most common etiologic factor in 315 (78.4%) patients admitted to the hospital for AP before the COVID-19 pandemic. Idiopathic pancreatitis was ranked second with 16.8%. While gallstone was the etiologic factor in 2 (28.6%) of seven patients who developed acute pancreatitis during COVID-19, hyperlipidemia was the factor for 1 (14.3%) patient. Moreover, the etiologic factor could not be determined in 4 (57.1%) patients, and they were regarded as idiopathic pancreatitis patients. It was observed that there was a significant difference in the incidence of idiopathic pancreatitis between patients with COVID-19 and

TABLE 1. Demographic data and clinical characteristics of acute pancreatitis patients with COVID-19 and non COVID-19.

Feature	COVID-19	Non COVID-19 acute pancreatitis
N	7	315
Age	51.4±12.5	57.17±19.1
Gender		
Female	3 (42.9%)	212 (67.3 %)
Male	4 (57.1%)	103 (32.7 %)
Exitus	0 (0.0%)	4 (1.2%)
Comorbid diseases		
HT	1 (14.3 %)	40 (12.7%)
DM	1 (14.3 %)	33 (10.4%)
CAD	–	24 (7.6%)
CRF	–	10 (3.1 %)
COPD	–	7 (2.2%)
Malignancy	–	2 (0.6 %)

DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, CRF:chronic renal failure, COPD: chronic obstructive pulmonary disease.

non-COVID-19. (*P*=0.015) (TABLE 2). Five patients with acute pancreatitis with COVID-19 had computed tomography for diagnosis or follow-up during the pancreatitis attack. According to the Baltahazar classification, one patient was moderate, and the others were mild pancreatitis. Considering Atlanta classification, pancreatitis was mild in five patients and moderate in two patients. Finally, all patients recovered with treatment (TABLE 3).

DISCUSSION

An increasing number of pancreatitis cases have been reported in the literature developed during or after COVID-19 infection⁽⁸⁻¹¹⁾. In addition, it was stated that pancreatic damage occurs parallel with the severity of the disease in COVID-19 patients. It was acknowledged that 1–2% of mild COVID-19 patients and 17% of severe COVID-19 patients had pancreatic damage⁽¹²⁾. In another study, amylase and lipase elevations were reported to range from 8.5% to 17.3% in COVID-19 patients. Likewise, enzyme elevation was observed to be correlated with the severity of COVID-19^(13,14). However, it has not been fully revealed if this enzyme elevation expresses clinical pancreatitis. On the other hand, focal pancreatitis was detected in significant numbers of the patients in autopsy studies^(15,16). In the COVID PAN study investigating the severity of pancreatitis in patients with COVID-19, the rate of idiopathic pancreatitis was higher in patients with COVID-19 than in the control group, 24% 14%, respectively⁽¹⁷⁾.

The incidence of acute pancreatitis is reported to be approximately 40–50/100,000⁽¹⁸⁾. In hospitalized COVID-19 patients, AP occurred two times higher than the rate stated above (0.1%). Supporting the related literature, in this study, we observed that AP developed in 0.1% of the patients hospitalized with COVID-19. Etiology was not found in 4 (57.1%) of these APs and was regarded as idiopathic pancreatitis. The rate of idiopathic pancreatitis was 16.8% in 315 patients diagnosed with AP in our hospital before the COVID-19 pandemic. However, the rate of idiopathic pancreatitis was higher in patients with COVID-19, and the difference was statistically significant. Although there is no evidence between COVID-19 and acute pancreatitis, data suggests that the SARS-Cov-2 virus may also play a role in the etiology of APs.

Since the beginning of the epidemic, COVID-19 has spread extensively all over the world. Therefore, we emphasize the importance of considering acute pancreatitis as a new etiological factor of the SARS-Cov-2 virus. Furthermore, to reveal the relationship between COVID-19 and AP, further multicenter, randomized, and controlled studies are needed.

TABLE 2. Etiological causes of patients with acute pancreatitis (COVID-19 and non-COVID-19).

Etiology	Non-covid pancreatitis	COVID19+ pancreatitis	<i>P</i> value
Biliary	247 (78.4 %)	2 (28.6%)	0.009
Idiopathic	53 (16.8%)	4 (57.1 %)	0.015
Hyperlipidemia	3 (0.9 %)	1 (14.3%)	0.020
Post ERCP	6 (1.9 %)	–	–
Drugs	4 (1.2 %)	–	–
Other	2 (0.6 %)	–	–
Total	315 (100 %)	7 (100 %)	

ERCP: endoscopic retrograde cholangiopancreatography.

TABLE 3. Demographic and biochemical characteristics of patients who developed acute pancreatitis during COVID-19.

Feature	Patient-1	Patient-2	Patient-3	Patient-4	Patient-5	Patient-6	Patient-7	Total
Age	71	57	60	33	42	51	46	51.4±12.5
Gender F/M	M	F	M	F	M	F	M	3/4
Atlanta	Mild	Mild	Mild	Mild	Moderate	Mild	Moderate	
Etiology	Idiopathic	Bilier	Bilier	Idiopathic	Hiperlipidemi	Idiopathic	Idiopathic	
CT (Balthazar)	2	–	–	2	5	1	3	
Amylase (U/L)	3510	2755	972	1246	188	3306	2070	2006±1256
Lipase (IU/L)	1662	1229	578	729	39	1662	1144	1006±595
ALT (IU/L)	18	238	305	23	19	105	66	110±115
AST (IU/L)	90	207	273	40	28	188	74	128±93
ALP (IU/L)	53	279	302	80	98	79	101	141±103
GGT (IU/L)	28	317	448	19	35	16	23	126±178
LDH (IU/L)	317	507	439	208	261	335	252	331±107
T.Bil (mg/dL)	0.8	2.6	2.1	0.9	0.8	0.7	1.0	1.27±0.75
D.Bil (mg/dL)	0.3	1.9	1.7	0.3	0.2	0.2	0.3	0.70±0.75
Glucose (mg/dL)	134	280	143	120	178	116	95	152±61
Urea (mg/dL)	42	38	45	27	30	78	50	44.2±16.9
Creatinine (mg/dL)	0.7	0.6	0.8	0.9	0.6	1.3	1.0	0.84±0.25
Calcium (mg/dL)	8.2	8.8	9.5	9.1	8.0	9.0	8.6	8.74±0.52
Triglyceride (mg/dL)	328	205	277	172	1758	253	195	455±576
WBC (cell/µmL)	4600	10500	7700	16000	10200	13500	6800	9900±3940
Neutrophil (cell/µmL)	3700	8900	6300	13900	8100	11100	5500	8214±3477
Lymphocyte (cell/µmL)	660	970	1120	1660	1700	1380	720	1187±405
CRP (mg/L)	108	23	75	59	37	43	177	74.5±53.1

CT: computerized tomography; ALT: alanina aminotransferase; AST: aspartato aminotransferase; ALP: fosfatase alcalina; GGT: gama glutamil transpeptidase; LDH: lactato desidrogenase; T.Bil: bilirubin; D.Bil: direct bilirubin; WBC: white blood cells; CRP: C-reactive protein.

Authors' contribution

Ebik B: idea/concept, data collection and processing. Ekin N: design, analysis, interpretation and manuscript writing. Bacaksız F: supervision/consultancy, literature review, materials, critical and review.

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RESUMO – Contexto – Infecções virais podem causar pancreatite aguda (PA). A pancreatite idiopática tem uma proporção importante na etiologia da pancreatite aguda. **Objetivo** – Investigar a taxa de desenvolvimento de pancreatite aguda em pacientes com COVID-19 e determinar a taxa de pancreatite idiopática na etiologia desta pancreatite. **Métodos** – No estudo foram incluídos 6.467 pacientes internados com o diagnóstico de COVID-19. Foram identificados pacientes diagnosticados com PA com base nos critérios de Atlanta. Fatores etiológicos foram determinados em pacientes que desenvolveram pancreatite aguda e comparados com os fatores etiológicos em 315 pacientes sem COVID-19, hospitalizados com o diagnóstico de PA antes da pandemia COVID-19. A PA foi detectada em 0,1% dos pacientes com COVID-19. Enquanto o cálculo biliar foi o fator etiológico em 2 (28,6%) dos sete pacientes que desenvolveram pancreatite aguda durante o COVID-19, a hiperlipidemia foi o fator para 1 (14,3%) paciente. Além disso, o fator etiológico não pôde ser determinado em 4 (57,1%) pacientes, sendo considerados pacientes com pancreatite idiopática. A pancreatite biliar foi o fator etiológico mais comum em 315 (78,4%) pacientes internados no hospital para PA antes da pandemia COVID-19. A pancreatite idiopática ficou em segundo lugar com 16,8%. **Conclusão** – Observou-se que houve diferença significativa na incidência de pancreatite idiopática entre pacientes com COVID-19 e não COVID-19 ($P=0,015$). Os resultados sugerem que o vírus SARS-Cov-2 pode estar entre os fatores que levam à pancreatite aguda.

Palavras-chave – COVID-19; pancreatite aguda; incidência aguda de pancreatite; etiologia.

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