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The Frequency of Pancreatic Enzyme Elevations and Effect on Disease Severity in COVID-19

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ABSTRACT

Aim: In this study, we aimed to evaluate the frequency of pancreatic enzyme elevations in COVID-19-infected patients and to examine the effect on disease severity.

Material and Methods: A total of 1249 patients who hospitalized with COVID-19 infection were included. The frequency of pancreatic enzyme elevations and the effect on disease severity in patients infected with COVID-19 were investigated.

Results: The pancreatic enzyme elevations (amylase/lipase or both) were detected in 32 of 1249 patients (incidence 2.96%). 32 cases with a mean age of 64.97±5.63 years were included in this study. 30 (93.75%) of the cases were men's gender. 31 (96.87%) of them had elevated amylase levels, 26 (81.25%) had elevated lipase levels and 25 (78.12%) of them had elevated both amylase and lipase levels. Only 10 (31.25%) of them tested radiological for acute pancreatitis (AP) and there was no radiological finding compatible with AP in any of the limited numbers of abdominal computerized tomography scans performed. 18 (56.25%) of the patients were transferred to the intensive care unit due to clinical worsening and mortality developed in 13 (40.62%) patients. The mean age of the deceased cases was 66.4±6.6 years and there was no statistically significant difference between deceased and survived COVID-19 patients (>0.05).

Conclusion: The median lymphocyte count was lower, and the median AST, ALT, and lipase levels were higher in the deceased group. Perhaps close clinical follow-up of patients with pathological findings in these values and radiological imaging, if necessary, may be beneficial in the method of the disease.

Keywords: COVID-19; disease severity; pancreatic enzyme elevations.

COVID-19'da Pankreatik Enzim Yüksekliklerinin Sıklığı ve Hastalık Şiddeti Üzerindeki Etkisi

ÖZ

Amaç: Bu çalışmada, COVID-19 ile enfekte hastalarda pankreatik enzim yükselmelerinin sıklığını değerlendirmek ve hastalık şiddetine etkisini incelemek amaçlanmıştır.

Gereç ve Yöntemler: COVID-19 enfeksiyonu ile hastaneye yatırılan toplam 1249 hasta dahil edildi. COVID-19 ile enfekte hastalarda pankreatik enzim yükselmelerinin sıklığı ve hastalık şiddeti üzerindeki etkisi araştırıldı.

Bulgular: 1249 hastanın 32'sinde pankreatik enzim yükselmeleri (amilaz/lipaz veya her ikisi) tespit edilmiştir (insidans %2,96). Bu çalışmaya yaş ortalaması 64,97±5,63 yıl olan 32 olgu dahil edilmiştir. Olguların 30'u (%93,75) erkek cinsiyetteydi. 31'inde (%96,87) amilaz, 26'sında (%81,25) lipaz, 25'inde (%78,12) hem amilaz hem de lipaz yüksekliği saptanmıştır. Bunların sadece 10'u (%31,25) akut pankreatit (AP) için radyolojik test yaptı ve yapılan sınırlı sayıdaki abdominal bilgisayarlı tomografi taramalarının hiçbirinde AP ile uyumlu radyolojik bulguya rastlanmamıştır. Hastaların 18'i (%56,25) klinik kötüleşme ve 13 (%40,62) hastada gelişen mortalite nedeniyle yoğun bakıma alınmıştır. Exitus vakalarının ortalama yaşı 66,4±6,6 yıldı; eksitus ve hayatta kalan COVID-19 hastaları arasında istatistiksel olarak anlamlı bir fark saptanmamıştır (p>0,05).

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Sonuç: Exitus grupta medyan lenfosit sayısı daha düşük, medyan AST, ALT ve lipaz seviyeleri daha yüksekti. Bu değerlerde patolojik bulguları olan hastaların yakın klinik takibi ve gerekirse radyolojik görüntüleme hastalığın yönteminde faydalı olabilir.
Anahtar Kelimeler: COVID-19; pankreatik enzim artışları; hastalık şiddeti.

INTRODUCTION

Acute pancreatitis (AP) is a very lethal inflammatory condition that affects the pancreatic tissue in a variety of ways, from mild edematous pancreatitis to severe necrotizing pancreatitis (1). AP in adults develops as a result of many different etiologies. It has been reported that it often develops as a result of the passage or compression of gallbladder stones. Other etiological factors are some viral infections, some metabolic-autoimmune diseases, alcoholism, drugs, and toxins (2). Viral pancreatitis has been most frequently associated with Mumps, Coksaki, Epstein-Barr virus, Measles, and rarely Hepatitis-A virus infections in the literature (3). Also, AP cases thought to be associated with the H1N1 Influenza virus have also been reported (4,5).

The Coronavirus disease-19 (COVID-19) pandemic has now killed more than 6 million people worldwide (6). The disease causes a wide range of symptoms, from asymptomatic infection to death. Although it mostly affects the respiratory system, it can also cause gastrointestinal symptoms such as nausea, vomiting, and diarrhea. One of the symptoms known to be linked to COVID-19 disease is gastrointestinal pain. The emergence of pancreatic enzyme elevation as a symptom of severe COVID-19 infection is poorly understood. Pancreatic enzyme elevations and, although rare, acute pancreatitis may develop in some COVID-19 patients and have been reported to be associated with particularly serious clinical outcomes (7-9). Angiotensin-converting enzyme 2 (ACE-2), a receptor for SARS-CoV, has been detected at a high rate in pancreatic islet cells, and it has been reported that this infection causes islet damage (9). Again, in a case series of 52 COVID-19 patients published in China, it was suggested that COVID-19 infection has a direct effect on pancreatic tissue, and pancreatic damage and lipase elevation were identified in 17% of active COVID-19 cases (10). McNabb-Baltar et al. (11) investigated lipase elevation and the presence of pancreatitis in 71 polymerase chain reaction (PCR)-confirmed COVID-19 patients in the United States (USA) and found hyperlipazemia in nine (12.1%) patients and lipase values three times higher than normal in two (2.8%) patients. However, none of the patients developed AP, and hyperlipazemia was not associated with a poor prognosis. It is stated that pancreatic organ damage in COVID-19 may result from direct viral involvement or from enzyme abnormalities in severe clinical conditions without significant pancreatic damage. Studies to date have not been able to definitively determine whether SARS-CoV-2 can cause pancreatic cell damage that leads to acute pancreatitis (12). The current consensus for the diagnosis of acute pancreatitis is as follows. The diagnosis can be made if two of these three requirements—abdominal pain that is consistent with AP, serum amylase/lipase counts that are larger than three times the upper limits of normal, and specific imaging findings are fulfilled (13). Possible AP mechanisms proposed in COVID-19 are as below;

a) Direct viral involvement: A moderate clinical picture of pancreatitis was identified as a consequence of respiratory failure or pancreatic damage caused by a cytopathic effect mediated directly by local SARS-CoV-2 replication or indirectly by a secondary systemic response, or as a result of an unfavorable immune response caused on by SARS-CoV-2 infection (10).

b) Enzymatic increase based on clinical parameters: pseudo pancreatitis, pancreatitis-like clinical syndrome: Secondary enzyme increases can be seen in this scenario (10).

c) Pancreatitis caused by drugs used in the treatment of drug-associated pancreatitis: Pancreatic damage can be seen in this clinical picture. Antipyretics are one of the agents found particularly guilty. Lopinavir and ritonavir used in the treatment are substrates of the p450 enzyme system, so they can cause many drug-drug interactions. Hepatitis or pancreatitis may develop as a result of the patient's drug regimen or as a side effect of the drug(s) (14–16). Methylprednisolone and dexamethasone, which are used in the treatment of COVID-19, can cause pancreatitis, albeit rarely (14-16). A link between AP and COVID-19 has been identified in case reports and retrospective cohort studies (14-17). Given that the pancreas expresses SARS-CoV-2 receptors and endothelial damage might result, this association is likely. However, this idea has several biases and requires additional examination (17).

In this study, we intended to identify the incidence of increased pancreatic enzymes in people with COVID-19 infection and to explore how this would impact the disease's severity.

MATERIAL AND METHODS

In this retrospective cohort study, patients hospitalized with the diagnosis of COVID-19 from 10 March 2020 to 01 July 2021, in the Infectious Diseases Clinic COVID-19 ward of our pandemic hospital were retrospectively analyzed. Our hospital is a tertiary care hospital in the northwest of Turkey. Having 220 beds dedicated solely to care for COVID-19 since March 23, 2020, the hospital was the main treatment for patients infected with SARS-CoV-2 in our region. In this retrospective study, hospitalized COVID-19 patients who met all inclusion criteria were included and those with elevated pancreatic enzymes were examined. Therefore, the sample size was not calculated.The Canakkale Onsekiz Mart University Faculty of Medicine's institutional review board approved this study (Approval Number: 04, KAEK-27/2022-2200053425). Because of the retrospective research design and the fast onset of this infectious illness, informed consent was waived.

Patients

The following were the inclusion criteria:

1. Age over 18 years;
2. Positive test result for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) of nasal and pharyngeal swab samples;

3. No missing medical records and computerized tomography (CT) scan records;
4. The hospitalized patients.

And also the following were the exclusion criteria:

1. Negative PCR test results for COVID-19;
2. Outpatients;
3. Pregnants;
4. Patients under the age of 18,
5. Missing data;
6. The patients who were previously treated at home due to COVID-19 were excluded.

The patients' demographic data, such as age, gender, length of hospital stay, treatments and duration of treatment, underlying conditions (previous operation, steroid use, non-steroidal immunosuppressive drug use, solid tumor, hematological tumor, diabetes mellitus, renal failure), neutropenia, history of liver disease, trauma, and so on), and physical examination findings were elevated. The outcome was defined as 30-day mortality after hospital admission. This information was transferred to case forms designed by the researchers.

The following tests were performed: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), urea, creatinine, albumin, amylase, lipase, and findings compatible with pancreatitis if any, recovery, and mortality/complications of the patient's developmental status. At the time of admission, laboratory values were collected from every patient who met inclusion criteria and examined.

The Real-Time (RT)-PCR assays for SARS-CoV-2 were carried out using kits provided by Turkey's Ministry of Health. All RT PCR analyses and biochemistry tests were performed by expert academics in the microbiology and biochemistry laboratories of our hospital. Leukocyte count, lymphocyte count, eosinophil, monocytes, hemoglobin, thrombocyte count, and MPV were studied in a complete blood count device (DXH800, Beckman Coulter, Miami, FL). ESR was measured by the Westergren method in the Vacuplus ESR120 device (Sistat, Ankara, Turkey). CRP was studied with the nephelometric method on the Image 800 device (Beckman Coulter, Miami, FL). Other biochemistry parameters were studied on the Cobas 6000 device (Roche Diagnostics, Mannheim, Germany).

Data Collection Tools

All information was obtained from the hospital information automation system and the patient's epicrisis.

Diagnosis of acute pancreatitis

The updated Atlanta criteria are used to make the diagnosis of AP (18).

The fulfillment of at least two of the three criteria provided as the diagnosis of AP.

1. Abdominal pain that resembled AP,
2. High amylase and/or lipase levels that are >3 times the upper limits of the normal range,
3. Radiological imaging of the findings

Statistical Analysis

The SPSS 20.0 packet software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. IBM Corp. Released 2012) was used to analyze the data. The Shapiro-Wilk normality test was used to determine whether the data were normally distributed. Descriptive statistics of the data were presented as n (%) and mean±standard deviation if the variable is normally distributed and median (minimum-maximum) otherwise. We used Student's t-test for comparisons of variables with normal distribution. Mann-Whitney U test was used for pairwise comparisons of variables that did not fit a normal distribution. The Kruskal-Wallis test was used to compare data belonging to more than one group. A p-value less than 0.05 was considered statistically significant.

RESULTS

This retrospective, observational study was conducted in Canakkale Provience, Turkey. A total of 1249 hospitalized COVID-19 patients were evaluated retrospectively during the study period. 30 (93.75%) of the cases were men's gender. 31 (96.87%) of them had elevated amylase levels, 26 (81.25%) had elevated lipase levels and 25 (78.12%) of them had elevated both amylase and lipase levels. Only 10 (31.25%) of them tested radiological for acute pancreatitis (AP) and there was no radiological finding compatible with AP in any of the limited numbers of abdominal computerized tomography scans performed. Table 1 provides a summary of the patient's demographic, clinical, and radiological characteristics.

In the study, 18 (56.25) of the patients were transferred to the intensive care unit due to clinical worsening and mortality developed in 13 (40.62) patients. The mean age of the deceased cases was 66.4±6.6 years and there was no statistically significant difference between deceased and survived COVID-19 patients (p= 0.324). The median lymphocyte count was lower, and the median AST, ALT, and lipase levels were higher in the deceased group (Table 2, Graphic 1, Graphic 2, and Graphic 3).

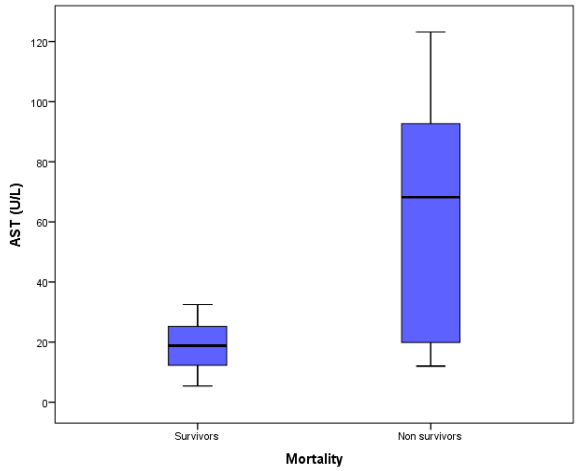
Table 1. The summary of the demographic, clinical and radiological features of the COVID 19 related AP cases

Variables	n (%)
Age (mean ± sd) (± years)	64.97±5.63
Gender (male)	30 (93.75)
Infiltration in thorax CT	32 (100)
Bilaterally infiltration in thorax CT	31 (96.87)
DM	11 (34.37)
HT	7 (21.87)
BMI >30	8 (25)
Elevation of amylase levels	31 (96.87)
Elevation of lipase levels	26 (81.25)
Elevation of both amylase and lipase levels	25 (78.12)
Abdominal pain resembling AP	26 (81.25)
Radiological evidence of AP	Not tested 27 (84.37) Tested, but no pathological findings 10 (31.25) Tested, detected pathological findings 0 (0)
Intubation	16 (50)
Transfer to intensive care unit	18 (56.25)
Mortality	13 (40.62)

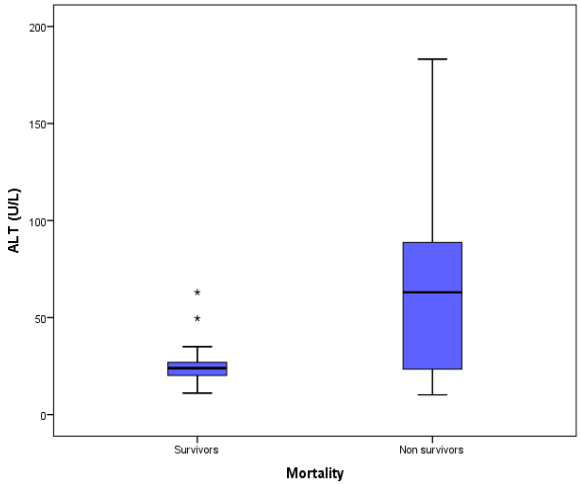
*mean ± sd: mean ± standard deviation, AP: acute pancreatitis, BMI: Body mass index, DM: diabetes mellitus, HT: hypertension.

Table 2. The comparsion of survivors and non survivors

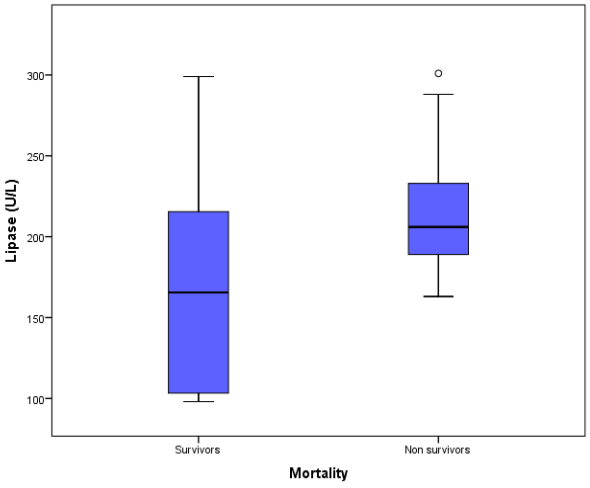
	Survivors (n=19)	Deceased (n=13)	p-value
Age (mean ± sd)	62.47±4.93	66.4±6.6	0.324
White blood cell count, 10^9 cells per L (min-max)	7.84 (4.1-11.3)	8.40 (3.7-18.9)	0.729
Lymphocyte count, 10^9 cells per L(min-max)	1.49 (0.41-1.83)	0.94 (0.5-1.12)	**0.001**
Haemoglobin, g/dL(min-max)	14.91 (11.2-16.1)	14.75 (11.7-15.9)	0.742
Lactate dehydrogenase, units per L (min-max)	313 (285-388)	348.5 (299-424)	0.364
INR (s) (min-max)	1.13 (0.9-1.78)	1.10 (0.7-1.52)	0.678
Platelet count ($\times 10^9$/L) (min-max)	227 (211-283)	202.5 (158-330.25)	0.556
D-dimer (µg/mL) (min-max)	185 (124-440)	246 (137-542.75)	0.143
ALT(IU/ml) (min-max)	23.90 (20-27.35)	63 (22.20-106.85)	**0.031**
AST (IU/ml) (min-max)	18.80 (12.25-25.25)	68.20 (17.90-93.35)	**0.009**
CRP (mg/dl) (min-max)	3.34 (0.68-9.11)	3.54 (0.65-5.9)	0.824
Glucose (mg/dl) (min-max)	113 (87.1141.2)	103.25 (84.68-131.35)	0.567
D.bilirubin (mg/dl) (min-max)	0.425 (0.212-0.708)	0.33 (0.25-0.58)	0.277
T.bilirubin (mg/dl) (min-max)	0.98 (0.66-1.11)	0.83 (0.68-1.22)	0.161
Magnezyum mg/dl (min-max)	1.98±0.20 (1.2-2.34)	2.03 (1.3-3.5)	0.348
Calcium (mg/ml) (min-max)	8.90 (7.6-9.1)	8.84 (7.2-10.4)	0.817
GGT U\L(min-max)	39 (13-52)	22 (12.75-24.75)	0.197
Amylase U\L (min-max)	222 (189-241)	204 (200.25-227.5)	0.811
Lipase U\L (min-max)	122.3 (102.3-203)	204 (187.75-235.75)	**0.014**
Albumin g/dl (min-max)	3.90 (3.38-4.24)	3.77 (3.28-4.05)	0.531
Trigliserid mg/ dl (min-max)	122.4 (84-190)	181.2 (127.95-234.93)	0.436



Graphic 1. The comparasion of AST levels between survivors and non survivors.



Graphic 2. The comparasion of ALT levels between survivors and non survivors.



Graphic 3. The comparasion of lipase levels between survivors and non survivors.

DISCUSSION

Despite advances in diagnostics and therapeutics, AP remains the greatest contributor to total medical costs and the 6th largest cause of in-hospital fatalities (19). Also, in the available literature, an increasing number of cases of pancreatitis occurring during or after COVID-19 infection have been described (2,9-14). In COVID-19 patients, pancreatic damage has been shown to occur in parallel with the severity of the illness (20-22). In this study, we aimed to evaluate the frequency of pancreatic enzyme elevations in COVID-19-infected patients and to examine the effect on disease severity.

According to a report, 17% of people with severe COVID-19 and 2% of patients with mild COVID-19 both have pancreatic damage (20). Amylase and lipase increases in COVID-19 patients were shown to range from 8.5-17.3% in another report (11,21). In our study, pancreatic enzymes were elevated (amylase, lipase, or both) in 32 out of 1249 patients (an incidence of 2.96%). All of the patients were mild COVID-19 patients. Due to the design of our study, patients with elevated pancreatic enzymes (amylase, lipase, or both) on the day of hospitalization were included in our study. Our reason for including patients on the day of hospitalization was to exclude pancreatitis caused by drugs used to treat drug-induced pancreatitis. Because it has been reported in previous studies that drugs such as favipiravir or steroid treatments used in our country in the treatment of COVID-19 can cause pancreatic enzyme elevation.

It is still unclear whether pancreatic enzyme elevations are associated with clinical pancreatitis. In previous autopsy series, localized pancreatitis was found in a large majority of COVID-19 cases (23,24). According to the Atlanta criteria, pancreatitis was diagnosed in just six (percentage of 1.89) of these patients in a similar study from Turkey (25). In this study, elevated amylase levels were shown to be substantially linked with the severity of COVID-19 in both univariate and multivariate models. Diabetes mellitus, renal failure, liver damage, hypotension, and sepsis were also observed to be linked with COVID-19 mortality 19 (25). In our study, the pancreatic enzyme elevations (amylase/lipase or both) were detected in 32 of 1249 patients (incidence 2.96%). 31 (96.87%) of them had elevated amylase levels, 26 (81.25%) had elevated lipase levels and 25 (78.12%) of them had elevated both amylase and lipase levels. Also, mortality developed in 13 (40.62%) patients in our study.

In two previous autopsy studies, focal pancreatitis with hemorrhagic and necrotic alterations in the pancreas was found in five of eleven (45.5%) and two of eight (25%) patients, respectively (23,24). But in our study, only 10 (31.25%) of them tested radiological for AP and there was no radiological finding compatible with AP.

Despite the possibility that elevated amylase and lipase levels have clinical significance, it seems highly unlikely that these measurements will be used as prognostic indicators in clinical practice. This is because enzyme elevation takes place during the intensive care period when the disease is advanced and mechanical ventilation is necessary, and this is when the disease may have clinical significance.

The majority of patients at this stage need vasopressor therapy due to single- or multi-organ failure (25).

In our study, only admission day's pancreatic enzymes were evaluated and their effects on the clinical course were investigated. There is no similar study in this context. The median lymphocyte count was lower, and the median AST, ALT, and lipase levels were higher in the deceased group, in our study. Perhaps close clinical follow-up of patients with pathological findings in these values and radiological imaging, if necessary, may be beneficial in the method of the disease.

CONCLUSION

In conclusion, despite the fact that ACE-2 receptors are widely expressed in pancreatic tissue, pancreatic enzyme increases associated with COVID-19 infection may be related to disease severity and hemodynamic instability. If the converse were true, we would have seen far too many cases of pancreatitis, owing to the pancreas's ACE-2 receptors. Even though the number of COVID-19 patients increasing, pancreatitis has remained in limited case reports.

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