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Association between pancreatic lipase levels and coronavirus disease-2019

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ABSTRACT

Aims: Elevated pancreatic enzyme can be observed in the course of coronavirus disease-2019 (COVID-19) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Here, we aimed to determine the frequency of lipase elevation in the course of COVID-19 and examine its effect on disease outcomes.

Methods: Of 42742 patients with the positivity of SARS-CoV-2 reverse transcriptase-polymerase chain reaction test (RT-PCR), 3167 undergoing lipase tests were included. The relationship between patients' clinical features, development of acute pancreatitis (AP), and mortality rates was investigated.

Results: Higher lipase levels than normal limits were found in 399 (12.6%) patients. Lipase levels were three times higher than the normal limit in 119 (3.8%) patients; compared to the rest of the patients, patients' age (62.8±17.9 vs 52.1±17.9 years, p<0.001), and rates of male patients (58% vs 45%, p=0.006) and mortality (17.6% vs 8%, p=0.001 respectively) were higher. Thirty-two (1.01%) patients were diagnosed with acute pancreatitis (AP). As lipase levels elevated, hospitalization (p<0.001) and requirement for intensive care unit (p=0.002) also increased. A total of 264 (8.3%) patients died, and mortality rates were higher in males (11% vs 6%, p<0.001). The dead were older (72.0±12.3 years vs 50.7±17.4 years, p<0.001). There was a linear positive correlation between patients' age (p<0.001), lipase levels (p<0.001), and mortality. Mortality was increased among men and in the presence of AP (p<0.001).

Conclusion: Pancreatic enzyme levels should be measured in the course of COVID-19 due to increased mortality in patients of advanced age, males with AP, and high lipase levels.

Keywords: Coronavirus disease 2019, COVID-19, lipase, pancreas, pancreatitis, SARS-CoV-2

INTRODUCTION

Although coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) primarily affects the respiratory and coagulation systems, the involvement of the gastrointestinal system at various levels, including endocrine and exocrine pancreas, can be observed in the course of the disease.[1-3] The elevation of pancreatic enzymes and the development of acute pancreatitis (AP) have been reported in the course of COVID-19 disease in both adults and children.[4-16] Although the exact mechanism is unknown, the SARS-CoV-2 virus enters cells via angiotensin-converting enzyme-2 (ACE-2) and transmembrane protease serine-2 (TMPRSS-2).[1] Compared to pancreatic islet cells, exocrine pancreatic ducts have been shown to express more ACE-2 and TMPRSS-2.[1] Acute pancreatitis is a serious clinical condition, and gallstones, alcohol, and such viruses as coxsackie B and mumps have often been blamed for its etiology.[17-19] Although SARS-CoV-2 is considered responsible for the etiology in a very small portion of the patients followed up due to the diagnosis of AP[20] it has been reported that the elevations of lipase and amylase are present at different levels in 1-2% of moderate and 17% of severe COVID-19 cases.[11-15] It has also been emphasized that the accompanying elevation of lipase in the course of COVID-19 is an indicator of the disease severity; those with hyperlipasemia are three times more likely to have severe COVID-19,[12] and those with high lipase levels have a higher risk of hospitalization.[10] On the other hand, the SARS-CoV-2 virus has been blamed in only one (2.3%) of 43 cases with AP.[20]

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In the present study, we aimed to determine the frequency of pancreatic enzyme elevation developing during the COVID-19 pandemic and to investigate its effect on the disease outcome.

METHODS

During the recent pandemic, our hospital served as a tertiary health facility where COVID-19 patients were diagnosed and treated. The cases where serum lipase levels were examined with positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test and followed-up due to COVID-19 between 31st March 2020, and 9th July 2021, were included in the analysis. The present study was retrospectively designed as a cohort study. The study was carried out with the permission of the Usak University School of Medicine Scientific Researches Evaluation and Ethics Committee (Date: 25.05.2022, Decision No: 89-89-12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In our hospital, a total of 42742 patients were diagnosed with the positivity of SARS-CoV-2 through the RT-PCR test during the study period. A total of 100453 lipase tests were performed in the study period. During the study period, lipase levels were measured by the spectrophotometric method using quinone staining with the Architect c 8000 model device (Abbott Diagnostic, Lake Forest, IL, USA). The reference limits for lipase levels were 13-60 U/L. The SARS-CoV-2 RT-PCR test results of 3167 cases were found to be positive, and after performing the measurements during the COVID-19 pandemic, 399 were determined to have higher lipase levels above the laboratory limit (>60 U/L). Therefore, the patients' group with "high lipase level" was created from these cases; 119 cases (3.8%, the rate among PCR positive patients was 0.27%) had higher lipase levels three times higher than the laboratory limit (≥180 U/L), and so the group with "three times higher lipase level" was created from these cases. The "control-1" group was constituted of the rest 2768 patients with normal lipase levels, and, the "control-2" group was composed of the rest 3048 patients with normal lipase levels and lipase levels three times lower than the upper laboratory limit. The cohort diagram of the study population is shown in Figure. The study was registered by the ClinicalTrials.gov Protocol and Results System (ClinicalTrials.gov identifier: NCT05601258).

Demographic features of the patients, such as age, gender, symptoms, and lipase levels on admission, and imaging methods were scanned from the hospital's automation system and recorded on the patient's charts. During the study period, the cases with AP were diagnosed through the device of computerized tomography (CT) (TOSHIBA Aquilion 16 CT Scanner in Kyoto, Japan) and the 1.5 T magnetic resonance imaging (MRI) scanner (Siemens Magnetom Aera, Erlangen, Germany) in our hospital. If the patients had at least two of the three features of the condition under the Atlanta Criteria, they were diagnosed with AP.[21] The "control 3" group was created from the 3135 patients whose lipase levels were monitored but didn't develop AP.

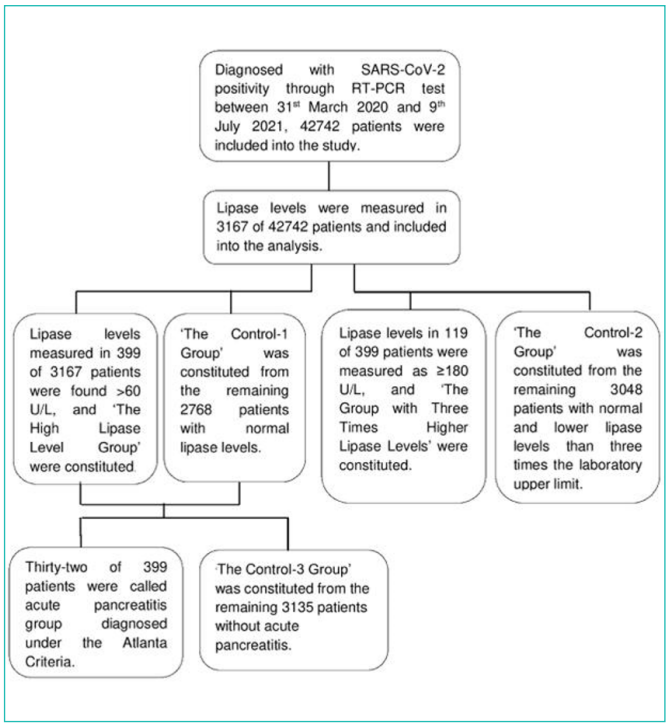

Figure. COHORT diagram of the study population

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, RT-PCR: Reverse transcriptase-polymerase chain reaction.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 25.0 (SPSS, IBM Corp., Armonk, NY, U.S., 2017). While the continuous data were expressed as mean±standard deviation (SD), the categorical data were referred to as percentages. In the comparison of the differences in terms of gender, mortality, and age levels in the groups with normal and high lipase levels, the Pearson chi-square test was used. However, in comparing the variables such as the time elapsed after the PCR test and age, the Mann-Whitney U test was used, considering the results of the Shapiro–Wilk normality test. A logistic regression model was created, in which lipase levels were considered normal (≤60) and high (>60) binary dependent variables, age, gender, and time elapsed after PCR test as independent variables. In addition to giving raw p values in Tables, the minimum statistical significance level was determined as 0.05.

RESULTS

Of 3167 patients included in the study, 399 (12.6%) (the rate was 0.9% among all SARS-CoV-2 PCR positive patients) had lipase levels above the laboratory upper limits; the group with "high lipase level" was constituted from these patients and compared with the "control-1 group" with lipase levels within normal limits. Both the descriptive statistics of the data and the relationships between lipase levels and other variables are given In Table 1. The age level of those in the group with "high lipase level" was higher than that of the controls (60.6±16.8 years vs 51.3±17.9, p<0.001, respectively). Considering the age variable categorically, a significant linear-by-linear association was found between the increasing age and lipase levels (p<0.001). The highest lipase levels were detected at 41.0±68.4 days after the positivity of SARS-CoV-2 PCR. The rate of male patients in the group with high lipase levels was higher than that in the control-1 (54.6% vs 44.6%, p=0.009). During the follow-up period, 263 patients (8.3%) died, and the mortality rate was higher in the group with high lipase levels [55 (13.8%) vs 208 (7.5%, respectively), p<0.001]. Given the findings of multivariate logistic regression analysis, the male gender was found to increase the risk 1.288 times more for the detection of high lipase, compared to female patients (p=0.046). In addition, considering the 18-24 age segment as the reference range, it was determined that the risk of encountering an increase in lipase levels increased in the 25-44 age, 45-59 age, 60-74 age, 75-90 age and >90 age categories (p=0.048, 0.007, <0.001, <0.001, and 0.007, respectively). (Table 2)

Table 1. Characteristics of patients with normal and high lipase levels

Variables	Normal lipase level Group/n (%) (%) 2768 (87.4)	High lipase level Group/n (%) (%) 399 (12.6)	p value
Sex			0.009[3]
Female	1533 (55.4%) (88.8%)	193 (48.4%) (11.2%)	
Male	1235 (44.6%) (85.7%)	206 (51.6%) (14.3%)	
Mortality			<0.001[3]
Survivors	2560 (92.5%) (88.2%)	343 (86.0%) (11.8%)	
Exitus	208 (7.5%) (78.8%)	56 (14.0%) (21.2%)	
Age (years)			<0.001[3]
18-24	189 (6.8%) (96.4%)	7 (1.8%) (3.6%)	
25-44	880 (92.8%) (89.3%)	68 (7.2%) (10.7%)	
45-59	766 (27.7%) (81.3%)	92 (23.1%) (18.7%)	
60-74	595 (21.5%) (77.6%)	137 (22.4%) (22.4%)	
75-89	316 (11.4%) (84.6%)	91 (22.8%) (15.4%)	
90+	22 (0.8%) (87.4%)	4 (1.0%) (12.6%)	
	Median (Min-Max)	**Median (Min-Max)**	
Time after PCR (days)	9 (0-382)	5 (2-103)	<0.001[4]
Age (years)	63 (18-94)	50 (18-99)	<0.001[4]

[1]In-group comparisons, [2]Intergroup comparisons, [3]Pearson chi-square test, [4]Mann Whitney U test, PCR: Polymerase chain reaction

Table 2. Characteristics of threefold high lipase levels of the study population

Variables	Lipase Levels: Lipase Normal+High n (%)1 (%)2 3048 (96.2)	Lipase Threefold High n (%)1 (%)2 119 (3.8)	p value
Sex			0.006[3]
Female	1676 (55.0) (97.1)	50 (42.0) (2.9)	
Male	1372 (45.0) (95.2)	69 (58.0) (4.8)	
Mortality			0.001[3]
Survivor	2805 (92.0) (96.6)	98 (82.4) (3.4)	
Exitus	243 (8.0) (92)	21 (17.6) (8)	
Age (years)			<0.001[3]
18-24	194 (6.4) (99)	2 (1.7) (1)	
25-44	927 (30.4) (97.8)	21 (17.6) (2.2)	
45-59	840 (27.6) (97.9)	18 (15.1) (2.1)	
60-74	691 (22.7) (94.4)	41 (34.5) (5.6)	
75-89	372 (12.2) (92.3)	35 (29.4) (7.7)	
90 +	24 (0.8) (96.2)	2 (1.7) (3.8)	
Clinical Spectrum			
No	-	86 (72.3)	
Abdominal pain	-	33 (27.7)	
Stones			
No	-	101 (84.9)	
Yes	-	18 (15.1)	
Imaging			
Negative	-	32 (26.9)	
Positive/ compatible with pancreatitis	-	13 (10.9)	
No imaging	-	74 (62.2)	
	Median (Min-Max)	**Median (Min-Max)**	
Time after PCR (days)	12 (0-382)	8 (0-244)	<0.0014
Age (years)	66 (18-94)	51 (18-99)	<0.0014

[1]In-group comparisons, [2]Intergroup comparisons, [3]Pearson chi-square test, [4]Mann Whitney U test, PCR: Polymerase chain reaction

In the group with lipase ≥3x, the age rate was higher in the patients' group than that in the controls (62.8±17.9 years vs 52.1±17.9 years, p<0.001), as well as including more male patients (58% vs 45%, p=0.006) (Table 2). While the mortality rates were 17.6% in the group with lipase ≥3x, the rates were found as 8% in the controls (p=0.001). As the age rate increased, lipase levels were detected to increase three times in more cases (p<0.001). Clinical findings, presence of gallstones, and imaging results only belonging to the group with three times higher lipase levels are given in Table 2. The time elapsed after PCR was longer in the group with lipase ≥3x (p<0.001). Given the findings of multivariate logistic regression analysis, it was observed that males were 1.641 times more likely than females to have lipase levels ≥3x (p=0.013). In addition, when the 18-

24 age group was taken as the reference, the probability of lipase levels ≥3x was found to increase 6,745 times between 60-74 years of age and 9,912 times between 75-90 years; however, lipase level was likely to be 9,833 times higher in the 90 and over age group (p=0.011, 0.002 and 0.030, respectively).

Thirty-two patients (in 1.01% of the cases where lipase levels were measured, and 0.07% of those with the positivity of PCR) were diagnosed with AP (Table 3). There was no difference in patients developing AP in terms of gender and mortality; however, it was found that AP patients were older, and the time elapsed after PCR was longer (p<0.001) (Table 3). When the multivariate logistic regression was performed, it was detected that the age rate and gender difference had no role in the development of pancreatitis, but only the increase in lipase levels was a risk factor for the development of pancreatitis [Odds ratio (OR) 1.005, 95% Confidence interval (CI) for OR lower-upper=1.003-1.007, p<0.001]. Hospitalization was evaluated only in those with high lipase levels. While the rate of hospitalization was found as 52.5% in the patients' group with lipase levels one to three times higher, the rate was 76.5% in those with three times higher lipase levels (p<0.001). Similarly, the requirement for the intensive care unit (ICU) was 12.1% in those with lipase levels one to three times higher while the rate was observed as 25.2% in the group with three times higher lipase levels (p=0.002).

Table 3. Clinical characteristics of patients with and without acute pancreatitis

Variables	Patients with AP 32 (1%) n (%)1 (%)2	Patients without AP (Control 3 Group) 3135 (99%) n (%)1 (%)2	p value
Sex			0.476[3]
Female	15 (46.9%) (0.9%)	193 (48.4%) (99.1%)	
Male	17 (53.1%) (1.2%)	206 (51.6%) (98.8%)	
Mortality			0.668[3]
Survivor	30 (93.7%) (1%)	2873 (91.6%) (99%)	
Exitus	2 (6.3%) (0.8%)	262 (8.4%) (99.2%)	
Age (years)			<0.001[3]
18-24	1 (3.1%) (0.5%)	195 (6.2%) (99.5%)	
25-44	6 (18.8%) (0.6%)	942 (30%) (99.4%)	
45-59	1 (3.1%) (0.1%)	857 (27.3%) (99.9%)	
60-74	10 (31.3%) (1.4%)	722 (23%) (98.6%)	
75-89	13 (40.6%) (3.2%)	394 (12.6%) (96.8%)	
90 +	1 (3.1%) (3.8%)	25 (0.8%) (96.2%)	
	Median (Min-Max)	**Median (Min-Max)**	
Time after PCR (days)	74.5 (0-382)	8 (0-256)	<0.001[4]
Age (years)	69.5 (22-94)	52 (18-99)	<0.001[4]

AP: Acute pancreatitis, [1]In-group comparisons, [2]Intergroup comparisons, [3]Pearson chi-square test, [4]Mann Whitney U test, PCR: Polymerase chain reaction

During the study period, 264 (8.3%) cases died, and the cases dying were seen to be older (72.0±12.3 years vs. 50.7±17.4 years, p<0.001), and the mortality rates were found higher in males (11% and 6% in males and females, p<0.001) (Table 4). Descriptive statistics of mortality are demonstrated in Table 4. Given the findings of multivariate logistic regression analysis, it was found that a one-year increase in age led mortality to increase by 8.5% (p<0.001), and male gender caused mortality to increase by 1.610 times (61%) (p=0.001). Considering normal lipase levels as the reference category, although high lipase levels increased the mortality rate 1.514 (51.4%) times compared to the normal limit, the increase did not reach a statistically significant level. On the other hand, while three times higher lipase levels increased the mortality rate 1.924 (92.4%) times compared to the normal limit (p=0.031), the presence of AP was detected to increase the mortality rate 2.136 times (p=0.033).

Table 4. Descriptive statistics of mortality accepted as a dependent variable

Variables	Exitus n (%)1 (%)2 264 (8.3)	Survivor n (%)1 (%)2 2903 (91.7)	p value
Sex			<0.001[3]
Female	105 (39.8) (6.1)	1622 (55.8) (93.9)	
Male	159 (60.2) (11)	1282 (44.2) (89)	
Age (yrs)			<0.001[3]
18-24	3 (1.1) (1.5)	193 (6.6)(98.5)	
25-44	5 (1.9) (0.5)	943 (32.5) (99.5)	
45-59	24 (9.1) (2.8)	834 (28.7) (97.2)	
60-74	105 (39.8) (14.3)	627 (21.6) (85.7)	
75-89	119 (45.1) (29.2)	288 (9.9) (70.8)	
90 +	8 (3) (30.8)	18 (0.6) (69.2)	
Lipase Levels			<0.001[3]
Normal	208 (78.8) (7.5)	2560 (88.2) (92.5)	
High	35 (13.3) (12.5)	245 (8.4) (87.5)	
Threefold High	21 (8.0) (17.6)	98 (3.4) (82.4)	
Clinical Spectrum			0.058[4]
No	19 (90.5) (22.1)	67 (68.4) (77.9)	
Abdominal Pain	2 (9.5) (6.1)	31 (31.6) (93.9)	
Stone			0.737[4]
No	19 (90.5) (18.8)	82 (83.7) (81.2)	
Yes	2 (9.5) (11.1)	16 (16.3) (88.9)	
Imaging			0.321[4]
Negative	4 (19) (12.5)	28 (28.6) (87.5)	
Positive/compatible with pancreatitis	1 (4.8) (7.7)	12 (12.2) (92.3)	
No imaging	16 (76.2) (21.6)	58 (59.2) (78.4)	
	Median (Min-Max)	**Median (Min-Max)**	
Time after PCR	9.5 (0-106)	9 (0-382)	0.177[5]
Age (years)	74 (18-94)	50 (18-99)	<0.001[5]

[1]Ingroup comparisons, [2]Intergroup comparisons, [3]Pearson chi square test, [4]Fisher exact test, [5]Mann Whitney U test

DISCUSSION

In the present study, it was detected that 12.6% of the patients whose lipase levels were measured during the COVID-19 pandemic had higher lipase levels than the upper limit of the normal; however, 3.8% had lipase levels three times higher than the upper limit of the normal. In addition, it was also found that there was a greater increase in lipase and mortality levels in males and elderly patients, and the presence of concomitant AP caused mortality to increase even further.

Although alcohol consumption and gallstones often come to the fore in the etiology of AP, many viruses may contribute to the development of AP through unknown mechanisms.[17-19] It has been reported that the invasion of pancreatic islet cells by viruses and the proliferation of the virus there may contribute to the development of diabetes mellitus (DM) and AP by triggering autoimmune events;[22] the SARS-CoV-2 virus has been blamed in only one (2.3%) of 43 cases diagnosed with AP.[20] Increased lipase levels developing in the course of SARS-CoV-2 infection due to AP cause lipotoxicity by leading to the breakdown of triacylglycerol from adipose tissues and increasing the release of unsaturated fatty acids, and have a toxic effect on mitochondria, which in turn causes the development of cytokine storm by increasing cytokine release, can be contributors.[23]

There are many studies evaluating lipase levels during the course of COVID-19. In the study where 756 patients with COVID-19 were evaluated by Hemant Goyal et al.[12] it was stated that the frequency of concomitant elevation in lipase levels was 11.7%; the cases with hyperlipasemia were 3.143 times more likely to have severe COVID-19, and therefore, high lipase levels are a determining criterion for the severity of COVID-19 along with the presence of AP. In another study involving 52 patients with COVID-19 pneumonia, Wang et al.[8] reported that although amylase or lipase levels were high in nine (17%) cases and the lipase levels were not three times higher than the upper laboratory limit. In another study by Barlass et al.[10] where 1003 patients with COVID-19 were included, and the lipase levels were measured in only 83 cases, the lipase levels were reported to be three times higher than the normal limit in 14 (16.8%) of the cases. In the present study, the lipase level was measured in only 7.4% of the patients undergoing PCR for SARS-CoV-2 within the relevant period. While the lipase level was higher in 0.9% and higher ≥3x in 0.27% of all PCR-positive patients than the normal limit, the lipase level was found to be higher in 12.6% and higher ≥3x than the normal limit in 3.8% of the cases where the lipase level was measured.

In the present study, 32 (1.01%) of 3167 patients evaluated through the measurements of the lipase levels were detected to have AP under the Atlanta Criteria. In a prospective study involving 316 patients with COVID-19 pneumonia, Akarsu et al.[13] stated that approximately 12.6% of the patients had AP; while no AP was witnessed in mild cases, 7.6% of severe cases and 32.5% of critical cases were found to have AP, and the rates of hospitalization and mortality were higher among those with AP.[13] In another study, however, Bulthuis et al.[4] reported that five (1.2%) of 433 patients with COVID-19 developed pancreatitis; all of the cases developing pancreatitis had also had severe COVID-19 disease, and three of the patients died. In the same study, the researchers suggested that in the development of AP, pancreatitis might be due to hypoperfusion rather than the direct effect of the virus. In the study where the patients with three times higher lipase levels were compared with those without by Barlass et al.[10] it was emphasized that intubation (78.6 and 23.5%, respectively) and requirement for ICU (92.9 and 32.8%, respectively) were higher among those with three times higher lipase levels.[10] Similarly, Akarsu et al.[13] determined that hospitalization and mortality rates were high in patients with COVID-19 developing AP. On the other hand, it was reported that the lipase levels were three times higher than the normal levels in 12 (31.6%) of 38 patients developing acute respiratory distress syndrome due to COVID-19; however, none of the patients displayed pancreatic pathology in imaging and were not diagnosed with AP, and the elevation of lipase may have also been related to the deterioration in microcirculation due to severe disease[15]. In the present study, it was found that increased lipase levels led to an increase in hospitalization and requirement for ICU; even three-quarters of the patients with three times higher enzyme levels required hospitalization; mortality rates were higher among male patients and the elderly, and mortality rose linearly with an increase in lipase levels. (**Tables 5** and **6**). In the present study, when the patients were categorized concerning their age levels, and each group was compared with the reference age segment of 18-24 years, it was found that the risk of encountering high lipase levels increased in each age group; the risk of having three times higher lipase levels than the normal was even higher, especially in the patients aged 60 years and above, and even the risk increased up to ten times in those at the age of 75 years and over. However, although lipase levels increased with age, and lipase levels were higher in males, we detected no effects of age and gender on the development of AP. On the other hand, the presence of AP was seen to cause a 2.1-fold increase in mortality.

Table 5. Clinical characteristics of patients with and without acute pancreatitis

Variables	Patients with AP 32 (1%) n (%)1 (%)2	Patients without AP (Control 3 Group) 3135 (99%) n (%)1 (%)2	p-value
Sex			0.476[3]
Female	15 (46.9%) (0.9%)	193 (48.4%) (99.1%)	
Male	17 (53.1%) (1.2%)	206 (51.6%) (98.8%)	
Mortality			0.668[3]
Survivor	30 (93.7%) (1%)	2873 (91.6%) (99%)	
Exitus	2 (6.3%) (0.8%)	262 (8.4%) (99.2%)	
Age (years)			<0.001[3]
18-24	1 (3.1%) (0.5%)	195 (6.2%) (99.5%)	
25-44	6 (18.8%) (0.6%)	942 (30%) (99.4%)	
45-59	1 (3.1%) (0.1%)	857 (27.3%) (99.9%)	
60-74	10 (31.3%) (1.4%)	722 (23%) (98.6%)	
75-89	13 (40.6%) (3.2%)	394 (12.6%) (96.8%)	
90 +	1 (3.1%) (3.8%)	25 (0.8%) (96.2%)	
	Median (Min-Max)	**Median (Min-Max)**	
Time after PCR (days)	74.5 (0-382)	8 (0-256)	<0.001[4]
Age (years)	69.5 (22-94)	52 (18-99)	<0.001[4]

AP: Acute pancreatitis, [1]In-group comparisons, [2]Intergroup comparisons, [3]Pearson chi-square test, [4]Mann Whitney U test, PCR: Polymerase chain reaction

Table 6. Rates of patients with high and ≥3X levels of lipase in need of hospitalization and admission to the intensive care unit

		Lipase Levels One-threefold High	Lipase Levels ≥3X High	p value
Hospitalization n (%)1 (%)2	Yes	133 (47.5) (82.6)	28 (23.5) (17.4)	<0.001
	No	147 (52.5) (61.8)	91 (76.5) (31.2)	
Admission to ICU n (%)1 (%)2	Yes	246 (87.9) (73.4)	89 (74.8) (26.6)	0.002
	No	34 (12.1) (53.1)	30 (25.2) (46.9)	

ICU: Intensive care unit

In the present study, we demonstrated that 8.3% of the patients with high lipase levels died; the mortality rate was higher in the males and the elderly, and the mortality increased linearly with increasing age. It is known that COVID-19 becomes more symptomatic with advancing age and is more fatal in the elderly.[11,13,24] Akarsu et al.[13] reported that while the female gender was dominant in the cases with mild COVID-19 pneumonia, the male gender was dominant in severe cases; AP was seen higher in those with high involvement in thorax CT; O_2 saturation was also lower in the cases with AP than the controls, and while the support of O_2, need for mechanical ventilation and requirement for ICU were higher, the length of hospital stay was longer, and the mortality was higher (32.5% vs 7.9%, respectively); however, it was reported that there was no effect of gender differences on the development of AP and mortality. On the other hand, in the study by Barlas et al.[10] the patient group with three times higher lipase levels was reported to include more male patients (78.6% vs 38.3%) than those with normal and lower lipase levels. In a retrospective cohort study conducted in our clinic, which is one of the first studies on the subject, we determined that 15.7% of COVID-19 patients whose lipase levels were measured had higher lipase levels than the normal limit; AP developed in only two patients, and the presence of the history of DM increased the risk of encountering hyperlipasemia 4.63 times.[6] In addition, we also determined in the same study that the patients with hyperlipasemia had lower oxygen saturation, higher C-reactive protein (CRP) and D-dimer levels, higher length of hospital stay, and higher requirement for ICU on admission.[6]

Limitations

SARS-CoV-2 is a novel virus not well-known by physicians. Therefore, although some physicians treating and following up COVID-19 patients in our hospital ordered pancreatic enzymes to be measured whether or not the patients had the symptoms suggestive of pancreatic pathology, such factors as the fact that other physicians did not order these tests, periodic monitoring of enzyme levels was not performed in some cases with elevated enzyme levels, or pancreatic imaging has yet to be performed are the limitations of the study. As another limitation, although it is known that many drugs, such as steroids and antibiotics, may contribute to the development of AP,[25] we included none of these drugs in the present analysis. The possibility that the physicians were unwilling to stay face-to-face with the patients for a long time due to the concerns about virus contamination during the SARS-CoV-2 pandemic, and the disease symptoms and other symptoms such as abdominal pain and nausea were ignored to be questioned in detail can also be regarded as another limitation of the study.

CONCLUSION

The SARS-CoV-2 virus can affect the pancreas, as well as many organs and tissues. Although the risk of detecting elevated lipase levels is high, especially in the elderly and male patients in the course of SARS-CoV-2 virus infection, and the relationship between age and gender, and the development of AP has yet to be demonstrated, it will be appropriate to measure the pancreatic enzymes even in the slightest suspicion in the course of COVID-19 to detect the pancreatic pathology at an earlier period in AP patients and those with high lipase levels due to the increased mortality, even if there are no typical symptoms.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Uşak University Faculty of Medicine Scientific Researches Evaluation and Ethics Committee (Date: 25.05.2022, Decision No: 89-89-12).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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REFERENCES

1. Muller JA, Gross R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab.* 2021;3(2):149-165.
2. Sinonquel P, Aerts M, Badaoui A, et al. BSGIE survey on COVID-19 and gastrointestinal endoscopy in Belgium: results and recommendations. *Acta Gastroenterol Belg.* 2020;83(2):344-354.
3. Moreels TG. COVID-19 and gastrointestinal endoscopy in Belgium: uncertainty and ambiguity. *Acta Gastroenterol Belg.* 2020;83:337-338.
4. Bulthuis MC, Boxhoorn L, Beudel M, et al. Acute pancreatitis in COVID-19 patients: true risk? *Scand J Gastroenterol.* 2021;56(5):585-587.
5. Suchman K, Raphael KL, Liu Y, Wee D, Trindade AJ, Northwell COVID-19 Research Consortium. Acute pancreatitis in children hospitalized with COVID-19. *Pancreatol.* 2021;21(1):31-33.
6. Akkus C, Yilmaz H, Mizrak S, Adibelli Z, Akdas O, Duran C. Development of pancreatic injuries in the course of COVID-19. *Acta Gastroenterol Belg.* 2020;83(4):585-592.
7. de-Madaria E, Siau K, Cardenas-Jaen K. Increased amylase and lipase in patients with COVID-19 pneumonia: don't blame the pancreas just yet! *Gastroenterol.* 2021;160(5):1871.
8. Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic injury patterns in patients with Coronavirus Disease 19 pneumonia. *Gastroenterol.* 2020;159(1):367-370.
9. McNabb-Baltar J, Jin DX, Grover AS, et al. Lipase elevation in patients with COVID-19. *Am J Gastroenterol.* 2020;115(8):1286-1288.
10. Barlass U, Wiliams B, Dhana K, et al. Marked elevation of lipase in COVID-19 disease: a cohort study. *Clin Transl Gastroenterol.* 2020;11(7):e00215.
11. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in the pancreas may cause pancreatic damage after SARS-CoV-2 infection. *Clin Gastroenterol Hepatol.* 2020;18(9):2128-2130.
12. Goyal H, Sachdeva S, Perisetti A, Mann R, Inamdar S, Tharian B. Hyperlipasemia and potential pancreatic injury patterns in COVID-19: a marker of severity or innocent bystander?. *Gastroenterol.* 2021;160(3):946-948.
13. Akarsu C, Karabulut M, Aydin H, et al. Association between acute pancreatitis and COVID-19: could pancreatitis be the missing piece of the puzzle about increased mortality rates? *J Invest Surg.* 2022;35(1):119-125.
14. Ding P, Song B, Liu X, et al. Elevated pancreatic enzymes in ICU patients with COVID-19 in Wuhan, China: a retrospective study. *Front Med.* 2021;8:663646.
15. Rasch S, Herner A, Schmid RM, Huber W, Lahmer T. High lipasemia is frequent in COVID-19-associated acute respiratory distress syndrome. *Pancreatol.* 2021;21(1):306-311.
16. Bacaksiz F, Ebik B, Ekin N, Kilic J. Pancreatic damage in COVID-19: why? how?. *Int J Clin Pract.* 2021;75(10):e14692.
17. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med.* 2009;169(11):1035-1045.
18. Toouli J, Brooke-Smith M, Bassi C, et al. Guidelines for the management of acute pancreatitis. *J Gastroenterol Hepatol.* 2002;17(Suppl):S15-S39.
19. Rawla P, Bandaru SS, Vellipuram AR. Review of infectious etiology of acute pancreatitis. *Gastroenterol Res.* 2017;10(3):153-158.
20. Yawar B, Marzouk A, Ali H, et al. Acute pancreatitis during COVID-19 pandemic: an overview of patient demographics, disease severity, management, and outcomes in an acute district hospital in Northern Ireland. *Cureus.* 2021;13(10):e18520.
21. Banks PA, Bollen TL, Dervenis C, et al. Acute Pancreatitis Classification Working G. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013;62:102-111.
22. Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and autoimmunity: a review on the potential interaction and molecular mechanisms. *Viruses.* 2019;11(8):762.
23. Hegyi P, Szakacs Z, Sahin-Toth M. Lipotoxicity and cytokine storm in severe acute pancreatitis and COVID-19. *Gastroenterol.* 2020;159(3):824-827.
24. Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. *Gastroenterol.* 2020;159(1):81-95.
25. Nango D, Nakashima H, Hirose Y, Shiina M, Echizen H. Causal relationship between acute pancreatitis and methylprednisolone pulse therapy for fulminant autoimmune hepatitis: a case report and review of the literature. *J Pharm Health Care Sci.* 2018;4(1):14.