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Hyperlipasemia is a poor prognostic factor in patients with COVID-19

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ABSTRACT

Introduction: COVID-19 disease may pose a considerable health threat to healthy individuals and individuals with comorbidity. The SARS-CoV-2 virus affects the respiratory tract and may cause damage to the pancreas by binding to the ACE-2 receptor in the pancreas. In our study, we investigated the effects of hyperlipasemia on morbidity and mortality in patients diagnosed with COVID-19.

Material and Method: In this study, 2350 patients diagnosed with COVID-19 between November 2020 and December 2020 were retrospectively reviewed. Other possible causes of hyperlipasemia were excluded. Hyperlipasemia secondary to COVID-19 was detected in 338 patients. These patients were divided into two groups based on their lipase elevation rates.

Results: Hyperlipasemia was detected in 14.4% of the patients diagnosed with COVID-19, and severe hyperlipasemia (>3x) was detected in 2.3%. The mean age of the patients was 64±13.8 (18-92), of which 59.5% (201) were male. In our study, 24 patients (1%) were diagnosed with acute pancreatitis. When compared according to lipase level, a significant difference was found between the groups regarding the history of HT, CCI score, development of ARF at follow-up, development of ARDS, need for ICU hospitalization, need for intubation, length of stay in ICU, and death rates. A weak correlation was found in the correlation analysis between hyperlipasemia and ARDS development and mortality.

Conclusion: Elevated lipase levels were associated with poor prognosis and mortality in patients with COVID-19 infection.

Keywords: SARS-CoV-2, hyperlipasemia, COVID-19, pancreatitis, viral pancreatitis

INTRODUCTION

The SARS-COV-2 virus has been spreading rapidly worldwide and has threatened all humanity (1). The course of the disease may range from subclinical infection to hospitalization and death (2). As of August 22, 2021, the cumulative number of cases reported globally in the COVID-19 pandemic is roughly 210 million, and the cumulative number of deaths is just over 4.4 million (3). The SARS-CoV-2 virus mostly affects the respiratory tract (2). However, symptoms, such as nausea, vomiting, abdominal pain, and diarrhea, in some patients suggest that the virus also affects the gastrointestinal system (GIS) (4).

Acute pancreatitis (AP) is an inflammatory disease of the pancreas. The clinical spectrum of AP ranges from mild edematous pancreatitis to severe necrotizing pancreatitis (5). There are various causes of acute pancreatitis in adults. Gallstones are the most common cause of acute pancreatitis. Other causes of pancreatitis include alcohol use, some metabolic disorders, autoimmune diseases, viral infections, exposure to drugs and toxins (5-6). Many viral, bacterial and parasitic infectious agents may cause AP (5). Diagnosis of infection-induced AP requires the absence of other potential causes of AP with evidence of active infection. It has been revealed that viruses, such as coxsackievirus, mumps, cytomegalovirus, hepatitis A, B, C, and Epstein-Barr virus, play a role in the etiology of AP (5). In studies conducted in patients with SARS-CoV-2 infection, ACE-2 expression was slightly higher in pancreatic tissue than in the lungs (7). Moreover, it has been reported that the SARS-CoV-2 virus may lead to pancreatic damage by binding to the ACE-2 receptor in the pancreas (7).

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In our study, we analyzed the correlation of hyperlipasemia with morbidity and mortality in patients diagnosed with COVID-19.

MATERIAL AND METHOD

Our hospital is a tertiary center for the diagnosis and treatment of patients with COVID-19 during the pandemic. This study was designed retrospectively. The diagnosis of COVID-19 was made by polymerase chain reaction (PCR) of nasopharyngeal swab samples. All patients over 18 who were positive for SARS-CoV-2 were included in the present study. A total of 2350 patients who underwent COVID-19 PCR testing and were diagnosed with COVID-19 between November 2020 and December 2020 were reviewed. Patients with known chronic renal failure and other causes of acute pancreatitis (biliary pancreatitis, hypertriglyceridemia, alcoholic pancreatitis, malignancy, hypercalcemia) that may be the cause of hyperlipasemia were excluded from this study. Three hundred thirty-eight patients with serum lipase levels above the upper limit of normal reference values were included in this study. One of the revised Atlanta diagnostic criteria is serum amylase and lipase levels >3 times the upper limit of normal. Hence, in our study, we divided the patients into two groups, considering the lipase elevation level as <3-fold (mild elevation) and >3-fold (severe elevation) (8). According to the revised Atlanta criteria, patients with at least two of the three criteria (abdominal pain consistent with pancreatitis, more than 3-fold increase in serum amylase-lipase levels, and appearance compatible with acute pancreatitis on radiological imaging) were diagnosed with AP. Our study was approved by the Amasya University Non-Interventional Clinical Researches Ethics Committee (Date: 18.02.2021, Decision No: E.5718) and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

The software of Statistical Package for Social Sciences (SPSS) (IBM SPSS Inc., Chicago, IL) for Windows 20 was used for our statistical analysis. Normality analysis of the data was evaluated via Kolmogorov-Smirnov and Shapiro-Wilk tests. When analyzing the study data, continuous variables with normal distribution were expressed as mean±standard deviation (SD), while continuous variables without normal distribution were expressed as median (min: max). In group comparisons, a parametric test (Student's t-test) was used for normally distributed continuous variables, whereas a non-parametric test (Mann-Whitney U test) was used for non-normally distributed variables. Fisher's exact test and Pearson's chi-square test were used for discrete variables. Spearman correlation coefficient was used to compute the correlation analysis. Statistical significance was considered $p \leq 0.05$ with a confidence interval (CI) of 95%.

RESULTS

Elevated lipase levels were detected in 14.4% of patients diagnosed with COVID-19, while severe lipase levels were detected in 2.3%. The ages of the patients ranged from 18 to 92, with a mean of 64±13.8% and 59.5% (201) male. All of the patients were hospitalized and followed up and treated. Demographic data of the cases are presented in **Table 1**. In the group with lipase >3 times higher, 22 patients had abdominal pain and one patient had pancreatitis on CT. The patient, whose CT was compatible with pancreatitis, did not have accompanying abdominal pain. In the group with lipase <3 times higher, 82 patients had abdominal pain and three patients had an appearance compatible with pancreatitis on CT. However, only one of the three patients whose CT was compatible with pancreatitis had abdominal pain. A total of 24 patients (n:2350, 1%) met the diagnostic criteria for acute pancreatitis according to the Revised Atlanta criteria.

Table 1. Demographic data of patients with elevated lipase

		Lipase Level Group (n:338)
Age		64±13.8 (22:92)
Gender (F/M)		137/201
BMI*		29.7±3.8
CCI		4.4±2.8 (0:12)
History of CAD [n/(%)]		118 (34.9)
History of DM [n/(%)]		127 (37.6)
History of HT [n/(%)]		229 (67.8)
History of KLD		1 (0.3)
Dyspnea [n/(%)]		322 (95.3)
Anorexia [n/(%)]		256 (75.7)
Nausea [n/(%)]		151 (44.7)
Diarrhea [n/(%)]		23 (6.8)
Abdominal pain [n/(%)]		104 (30.8)
Thorax CT severity (n:66/n:270)	<18 ≥18	236 (70.2) 100 (29.9)
Abdominal CT sign of pancreatitis		4 (1.1)
ARF		86 (25.4)
Lipase rising time		11.6 (1:42)
Length of ICU stay		2.4±5.5 (0:40)
Length of hospital stay		11.6±8.1 (0:50)
ARDS		98 (29)
Intubation		91 (26.9)
Requirement for ICU [n/(%)]		89 (26.3)
Mortality [n/(%)]		91 (26.9)

BMI : Body mass index, CCI: Charlson Comorbidity Index, CAD: coronary artery disease, DM : Diabetes mellitus, HT : Hypertension, CLD:Chronic liver disease, ICU: Intensive care unit, ARDS: Acute respiratory distress syndrome, ARF: Acute renal failure

Parameters, such as age, BMI, symptoms (dyspnea, anorexia, nausea, abdominal pain), thorax CT severity index and CORADS classification, appearance compatible with pancreatitis on abdominal CT, lipase elevation time, and duration of hospitalization were

similar in both groups (p> 0.05)). However, previous history of hypertension (HT), Charlson comorbidity index (CCI) score, development of acute renal failure (ARF) in follow-up, development of acute respiratory distress syndrome (ARDS), need for intubation, need for follow-up in the intensive care unit (ICU), duration of ICU stay and mortality rates were similar in both groups (**Table 2**).

When the groups were evaluated regarding laboratory parameters, urea, creatinine, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), direct bilirubin (DB), amylase, uric acid, ferritin, D-Dimer, protein, albumin, leukocytes, hemoglobin, hematocrit, platelets, and C-reactive protein (CRP) levels were significantly different in both groups (**Table 3**).

Table 2. Some clinical and demographic features in groups with high and low lipase levels

	High Lipase Level Group (n:68)	Low Lipase Level Group (n:270)	P
Age	67.4 (37:87)	62.6 (22:92)	0.03
Gender (F/M)	27/41	110/160	0.9
BMI	28.9±3.8	29.9±3.8	0.08
CCI	5.5 (0:12)	4.17 (0:12)	0.001
History of CAD [n/(%)]	29 (42.6)	89 (33)	0.17
History of DM [n/(%)]	26 (38.2)	101 (37.4)	0.9
History of HT [n/(%)]	54 (79.4)	175 (64.8)	0.03
History of KLD	1 (1.5)	0	0.2
Dyspnea [n/(%)]	65 (95.6)	257 (95.2)	1
Anorexia [n/(%)]	54 (79.4)	202 (74.8)	0.52
Nausea [n/(%)]	37 (54.4)	114 (42.2)	0.07
Diarrhea [n/(%)]	8 (11.8)	15 (5.6)	0.1
Abdominal pain [n/(%)]	22 (32.4)	82 (30.4)	0.86
Thorax CT severity (n:66/n:270) <18 ≥18	47 (70.1) 20 (29.9)	189 (70.3) 80 (29.7)	1
Thorax CT-CORAD classification low risk high risk	15 (22.4) 52 (77.6	55 (20.4) 214 (79.6)	0.7
Abdominal CT sign of pancreatitis	1(1.5)	3 (1.1)	1
ARF	29 (42.6)	57 (21.1)	0.001
Lipase rising time	11 (1:29)	11.47 (1:42)	0.6
Length of ICU stay	3.2 (0:24)	2.2 (0:40)	0.006
Length of hospital stay	11.9 (0:50)	11.9 (1:41)	0.6
ARDS	32 (47.1)	66 (24.4)	0.001
Intubation	29 (42.6)	62 (23)	0.002
Requirement for ICU [n/(%)]	27 (39.7)	62 (23)	0.008
Mortality [n/(%)]	31 (45.6)	60 (22.2)	0.001
Steroid usage requirement	65 (95.6)	265 (98.1)	0.2
NSAID use	6 (8.8)	17 (6.3)	0.6

BMI : Body mass index, CCI: Charlson Comorbidity Index, CAD: coronary artery disease, DM : Diabetes mellitus, HT : Hypertension, CLD:Chronic liver disease, ICU : Intensive care unit, ARDS: Acute respiratory distress syndrome, ARF: Acute renal failure

A strong positive correlation was found between lipase elevation and amylase elevation. Furthermore, a weak positive correlation was found between hyperlipasemia and urea, creatinine, uric acid, d-dimer levels, ARDS development, and mortality, whereas a weak negative correlation was found between hyperlipasemia and albumin.

In the correlation analysis with mortality, a very strong positive correlation was found with ARDS, the need for intubation, and ICU admission A strong positive correlation was found between the duration of ICU stay and mortality. A moderate positive correlation was found with CCI score, development of ARF, urea, creatinine, LDH, CRP, and D dimer levels. A weak positive correlation was found with a previous history of HT, uric acid, DB, and ferritin levels. Moreover, a weak negative correlation was found with protein, albumin, and platelet levels (**Table 4**).

Table 3. Laboratory characteristics of groups with high and low lipase levels

	High Lipase Level Group (n:68)	Low Lipase Level Group (n:270)	P
Glucose	231.1 (60:701)	214.1 (41:1043)	0.4
Urea	110.4 (25:277)	63.4 (17:361)	0.001
Creatinin	1.99 (0.2:14)	1.13 (0.3:10.3)	0.001
ALT (0-55 U/L)	48.7 (9:448)	71.1 (3:1302)	0.15
AST (0-55 U/L)	37.5 (7:182)	52.8 (5:1080)	0.4
GGT (9-36 IU/L)	72.9 (11:297)	72.7 (5:861)	0.9
Alkaline phosphatase	83.7 (44:185)	80.3 (20:622)	0.02
LDH	476 (141:1359)	389.2 (57:1426)	0.001
Total Bilirubin	0.63 (0.19:6)	0.48 (0.11:2)	0.2
Direct Bilirubin	0.36 (0.03:4.6)	0.21 (0.01:0.9)	0.007
Amilaz	463.7 (205:1442)	100.4 (61:192)	0.001
Lipaz	463.7 (205:1442)	100.3 (61:178)	0.001
Uric acid	6 (1.2:19.5)	4.4 (1.1:13.4)	0.001
Triglyceride	170.3 (56:769)	201.3 (56:769)	0.12
Leukocyte	13408 (1630:41350)	11039 (2500:36030)	0.06
Hemoglobin	11.8± 2.1	12.8±1.8	0.002
Hematocrit	35±5.6	38.1±5.1	0.04
Platelet	230704 (66000:513000)	270306 (82000:601000)	0.01
CRP	64.4 (1.34:436)	35.6 (0.17:223)	0.01
Sedimentation	53.5 (9:144)	48.3 (4:135)	0.4
Fibrinogen	516.4 (185:1170)	486.9 (40-1200)	0.2
Ferritin	725.36 (49:3439)	651.8 (7:7591)	0.06
D-Dimer	1.92 (0.05:7.86)	1.5 (0.01:22.3)	0.001
Protein	5.84 (4.1:7.8)	6.1 (3.9:7.8)	0.03
Albumin	3.15 ±0.58	3.45±0.48	0.001

ALT : Alanine aminotranspherase, AST : Aspartate aminotranspherase, GGT : Gamma glutamil transpherase, LDH : lactate dehydrogenase. CRP : C-reactive proteine.

Table 4. Correlation analysis of lipase elevation and mortality and other parameters

	Lipase elevation amount		Mortality	
	r	P	r	p
CCI	0.188	0.001	0.523	0.001
HT	0.125	0.02	0.248	0.001
ARF	0.198	0.001	0.595	0.001
ARDS	0.200	0.001	0.920	0.001
Intubation	0.178	0.001	0.925	0.001
Requirement for ICU	0.152	0.005	0.818	0.001
Length of ICU stay	0.149	0.006	0.786	0.001
Mortality	0.211	0.001	1	
Urea	0.271	0.001	0.565	0.001
Creatinin	0.272	0.001	0.525	0.001
Uric acid	0.226	0.001	0.336	0.001
Protein	-0.132	0.03	-0.239	0.001
Albumin	-0.211	0.001	-0.36	0.001
Amylase	0.694	0.001	0.193	0.001
Lipase	0.694	0.001	0.193	0.001
Alkaline phosphatase	0.140	0.02	0.186	0.002
LDH	0.158	0.004	0.515	0.001
Direct bilirubin	0.148	0.006	0.322	0.001
Hemoglobin	-0.170	0.002	-0.165	0.002
Hematocrit	-0.156	0.004	-0.084	0.12
Platelet	-0.134	0.01	-0.375	0.001
CRP	0.135	0.01	0.490	0.001
Ferritin	0.100	0.06	0.271	0.001
D-Dimer	0.250	0.001	0.432	0.001

r=Spearman's Correlation Coefficient
CCI: Charlson Comorbidity Index, HT : Hypertension, ARF: Acute renal failure, ARDS: Acute respiratory distress syndrome, ICU : Intensive care unit, LDH : lactate dehydrogenase. CRP : C-reactive proteine.

DISCUSSION

Elevations in pancreatic enzymes have been reported in patients diagnosed with COVID-19 (9,10). However, lipase elevation is not unique to pancreatitis (11) and can be released from organs other than the pancreas (12). In renal failure, serum amylase and lipase levels increase due to decreased renal clearance (13,14). In addition to that, increased serum amylase and lipase levels have been reported after trauma, burns, diabetes mellitus, severe gastroenteritis, and cardiovascular surgery (13,14). Based on the Revised Atlanta Criteria, at least two of the three criteria (typical abdominal pain, elevated serum amylase and/or lipase values, and characteristic findings on abdominal imaging) are required to diagnose acute pancreatitis (8). According to the Revised Atlanta Criteria, pancreatitis is a well-known cause of organ failure (such as renal, respiratory and cardiovascular) (8,15). Many viruses may cause pancreatitis (16). However, it has not been fully elucidated whether SARS-CoV-2 directly impacts the pancreas or causes hyperlipasemia secondary to multi-organ failure (MOF) (17,18). Thus, in COVID-19, hyperlipasemia may be secondary to pancreatitis, MOF, or both (19). Studies have demonstrated that ACE-2 expression is higher in pancreatic tissue than in lungs in patients with SARS-CoV-2 infection. This may be a cause of pancreatic injury (7,20).-Pathophysiology of acute pancreatitis activated pancreatic enzymes and pancreatic ischemia secondary to microcirculation disorder of the pancreas play a key role (21). Case-based reports in the literature have revealed cases of acute pancreatitis secondary to COVID-19 (22,23,24). Besides, in the studies, the incidence of pancreatitis secondary to COVID-19 was 0.16%, 7.46%, and 17%, respectively (25,7,9). In our study, the incidence of pancreatitis was 1% (24/2350).

McNabb-Baltar suggested that hyperlipasemia in patients with COVID was not associated with severe illness or poor clinical outcomes. The author stated that hyperlipasemia is not caused by pancreatic injury but might be associated with other gastroenterological manifestations of the virus (11). Liu, on the other hand, argued that in patients with severe COVID-19 infection (even without necrotizing pancreatitis findings), taking pancreatic injury into consideration may impact the prognosis of patients(7). In addition, Lax et al. reported that 36% of patients with COVID-19 without clinical pancreatitis suspected had pancreatic parenchymal necrosis and focal pancreatitis findings (26). Meanwhile, Rasch suggested that pancreatic tissue damage may occur in severe COVID-19 patients, although there are no typical clinical symptoms (10).

In their study, Liu et al. (7) analyzed pancreatic injury due to SARS-CoV-2 infection. They determined elevations in both amylase and lipase levels in 1.85% of mild cases. An increase of 17.9% and 16.4% were detected in amylase and lipase levels of severe COVID-19 patients, respectively. Moreover, McNabb-Baltar detected hyperlipasemia in nine (12.1%) patients (11). In the study of Barlass et al. (19) involving 1003 COVID-19 patients, a >3-fold increase in lipase was found in 14 patients (83% out of 16.8%) . In our study, elevated lipase levels were detected in 14.4% of patients diagnosed with COVID-19, while severe lipase levels were detected in 2.3%.

In the study of Barlass et al. (19), there was a significant predominance of males in the high lipase group (78.6% vs. 38.8%); however, there was no difference regarding other demographic characteristics. Besides, in Rasch's study, it was reported that there was no significant difference between the group with high lipase levels and the control group regarding BMI (11). In our study, no difference was found between the groups regarding sex and BMI. However, patients in the group with severe lipase elevation were older and had a higher CCI score. Moreover, patients with a previous history of HT were more common in the group with severe lipase elevation (p: 0.03).

In the study of Barlas, it was revealed that nausea-vomiting symptoms were more common in the low lipase group (75.4% vs. 42.3%) (19). However, in our study, symptoms, such as shortness of breath, nausea, vomiting, anorexia, and abdominal pain, and the severity of pulmonary involvement secondary to COVID-19 on thoracic CT imaging were similar in both groups.

Liu reported that pancreatic changes were consistent with pancreatitis in five patients (7.46%) with severe disease findings on lung CT, but none of these patients had signs of acute necrosis in the pancreas (7). In the study of Rasch et al., typical pancreatitis imaging findings were not observed in any of the patients (10). In our study, abdominal CT imaging of one patient with severe lipase elevation and three patients with mild lipase elevation revealed enlargement of the pancreatic parenchyma and peripancreatic inflammation ($p>0.05$). On the other hand, in our study, pancreatic necrosis was not detected in any patient's abdominal CT imaging.

Many of the studies in the literature have reported a relationship between high lipase levels and worse clinical outcomes in COVID-19 disease (7,10,19). In the study of Rasch et al., the incidence of ARDS was higher in the group with serum lipase activity >180 U/l (p: 0.003). However, in the same study, it was revealed that there was no difference between the groups regarding ventilation duration and mortality (10). Barlass et al. reported higher ICU admission rates (92.9% vs. 32.8%) and intubation rates (23.5% vs. 78.6%) in the group with high (>3 ULN) lipase levels. In addition, in the study of Barlass, no correlation was found between high lipase levels and the duration of hospitalization (19). In our study, the development of ARF during the follow-up period, the development of ARDS, the need for hospitalization in the ICU, the length of ICU stay, and the mortality rates were higher in the group with severe lipase elevation (**Table 2**). Likewise, in our study, no difference was revealed between the groups regarding the duration of hospitalization. In the correlation analysis with the lipase elevation level, a weak positive correlation was found with amylase, urea, creatinine, uric acid, d-dimer levels, ARDS development, and mortality, whereas a weak negative correlation was found with albumin (**Table 4**).

The limitation of our study was that this study was designed retrospectively. Studies supported by autopsy findings could elucidate the exact cause of hyperlipasemia.

CONCLUSION

Studies support that COVID-19 does not cause a disease that only affects the lungs but a multisystemic disease. In many studies, it has been demonstrated that ARDS, ICU admission, and mortality are higher in patients with hyperlipasemia. Hyperlipasemia could be utilized as a marker for more severe disease and poor prognosis in the monitorization and treatment follow-up of patients with COVID-19 infection. Furthermore, the SARS-CoV-2 virus should be considered in the etiopathogenesis of acute pancreatitis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Amasya University Non-Interventional Clinical Researches Ethics Committee (Date: 18.02.2021; Decision No: E.5718).

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.

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