

# COVID-19 AND HYPERAMYLASEMIA

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## Abstract

**Object:** Our aim is to evaluate the elevation of pancreatic enzymes in COVID-19 patients and their relationship with severity of COVID-19. **Method:** In this study, 1378 patients with COVID-19 infection were included. Relation of elevated amylase and lipase levels and co-morbid conditions with the severity of COVID-19 were checked. The effect of hemodynamic parameters and organ failures on pancreatic enzymes and their relations with prognosis were statistically analyzed. **Results:** There were 678 (%49,2) female patients and 700 (50,8%) male patients. Of all patients, 687 (49,9%) had mild, 691 (50,1%) severe COVID-19 infections. Elevated amylase levels were detected in 23% of patients (n:316). 19% (261) of them had a slight (1-3 times) increase in amylase levels, while 4% (55) had a more than 3 times increase in amylase than normal. Only 6% of patients with elevated amylase levels had the acute pancreatitis according to Atlanta criteria. According to univariate and multivariate analyses, elevated amylase levels was found statistically related with severity of COVID-19 (OR:4,37-p <0,001). And also diabetes mellitus (DM) (OR:1,82-p:0,001), kidney failure (OR:5,18- p< 0,001), liver damage (OR:6,63 p < 0,001), hypotension (OR:6,86-p< 0,001), sepsis (OR:6,20-p:0.008) were found to related to death of COVID-19. **Conclusions:** Elevated pancreatic enzyme levels in COVID-19 infections is to related to severity of COVID-19 infection and hemodynamic instability. Similar to other organs, the pancreas can be affected by severe COVID-19 infection.

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**Key Words:** COVID-19, Pancreas, Amylase

### **What's already known about this topic?**

It has been suggested that Covid-19 can cause pancreatic damage. There are a limited number of studies related to the possibility of an increase in the level of amylase enzyme in Covid-19 patients.

### **What does this article add?**

Covid-19 does not directly cause pancreatic damage. Pancreatic enzyme elevation in patients with Covid-19 develops in the advanced stages of the disease due to multiorgan dysfunction and shock.

### **INTRODUCTION:**

COVID-19 infection, which was initially thought to affect only the upper respiratory tracts, can affect almost all systems, not just the respiratory system. This is due to the angiotensin-converting enzyme 2 (ACE 2) receptors, which coronavirus binds in to enter the cells. These receptors are also commonly available in the gastrointestinal system such as liver, pancreatic, colonic cells. <sup>1-2</sup>

Recent studies have shown that COVID-19 infection can cause damage to the pancreas due to the high expression of ACE2 receptors from the pancreatic tissue. <sup>3</sup> Additionally, it has been stated in another study that hyperglycemia can occur due to pancreatic islet cell damage in patients with COVID-19 and severe patients with COVID-19 should be followed up closely in terms of pancreatic damage. <sup>4-5</sup>

In this study, we evaluated the amylase and lipase elevations in patients with COVID-19. And additionally, we aim to research the relation between pancreatic enzyme elevations and severity of COVID-19 infection and to identify underlying conditions.

### **MATERIAL AND METHODS**

In this study, 1378 patients with COVID-19 infection between March-December in 2020 in our hospital were included. Signs such as fever, blood pressure, laboratory parameters, treatments, and co-morbid conditions were followed-up during the hospitalization. Next to these parameters, amylase and lipase levels were checked. Values above 105 U/l for amylase and 65 IU/L for lipase were considered high. <sup>6</sup> Patients with pancreatitis were diagnosed according to Atlanta criteria. <sup>7</sup>

Additionally, pancreatic enzyme elevation in COVID-19 infection related to the severity of disease was investigated. Patients were divided into two groups mild and severe COVID-19 infection. Patients with fever, headache, loss of taste and smell, generalized myalgia, and without tachypnea (Oxygen saturation >%92) were considered a mild infection. Patients on invasive or non-invasive respiratory support or with deteriorated hemodynamic conditions were considered severe COVID-19 infection. <sup>8</sup>

The causes of pancreatic enzyme elevation were questioned in patients with mild and severe COVID-19 infection and patients who died and recovered. The relation between elevated pancreatic enzymes and metabolic parameters, hemodynamic findings, single and multiple organ failures was examined. <sup>9-10</sup>

Mean arterial pressure was used to measure the hypotension. Mean arterial pressure between 60-110 mmHg as normal, below 60 mmHg as hypotension, above 110 mmHg was evaluated as hypertension. <sup>11</sup>

Liver damage was determined according to the EASL 2019 guidelines. <sup>12</sup> (ALT [?] 5 × ULN (Upper limit of normal) or ALP [?] 2 ULN (In the absence of known bone pathology) or ALT [?] 3 ULN with simultaneous increase of total bilirubin concentration [?]2 ULN). <sup>12</sup> Kidney injury was determined according to RIFLE criteria. <sup>13</sup>

This study was conducted in accordance with the Helsinki Declaration and permission was obtained from the hospital's ethics committee. (Issue number 611 dated 16.10.2020)

### **Statistical Analysis**

Kolmogorov-Smirnov, Shapiro-Wilk test, coefficient of variation, skewness, and kurtosis methods were used to check the normal distribution of patient data. Mean and Standard deviation values were specified for continuous variables, while categorical variables were expressed as a percentage (%). Student T-test and Mann-Whitney U test were used in paired groups to compare pancreatic enzymes and disorders of other organs between patients with severe and mild COVID-19 infection. ANOVA test was used for parameters homogeneously distributed in triple groups. Bonferroni correction was used to determine in which groups significant results were obtained. Welch ANOVA and Kruskal-Wallis tests were performed for the non-homogeneous parameters. Pearson and Spearman correlation analyses were performed for the relationship between pancreatic enzyme elevation and other parameters. Univariate and multivariate analyzes were performed to determine the factors associated with pancreatic enzyme elevation. All tests were bilateral and a p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS26.0 for Windows (SPSS Inc. Chicago, IL, USA) package program.

## RESULTS

A total of 1378 patients, 687 of them mild and 691 of them severe, were included in the study. 678 of patients (%49.2) were women; 700 of patients were male. There were significant difference between mild and severe COVID-19 patients in terms of laboratory parameters. Kidney failure, diabetes mellitus, ischemic hepatitis, sepsis were clearly higher in patients with severe COVID-19. Amylase and lipase levels were also higher in patients with severe COVID-19. (Table 1)

Amylase elevation at different levels occurred in 316 (%23) of 1378 patients with COVID-19. There were amylase elevations in 261 patients as much 1-3 times than normal and in 55 (%4) patients 3 times more than normal. Pancreatitis was detected in only 6 (%1.89) of these patients according to Atlanta criteria. Amylase and lipase elevation was found to related to severity of COVID-19 infection in the rest of all patients. And also diabetes mellitus, kidney failure, hypotension, ischemic hepatitis was found to related to mortality from COVID-19 infection. There were no relation between lymphopenia and elevated amylase levels. (Table-2) Those older than 65 years were more likely to have (1,89 times) elevated increased enzyme levels during the examination of causes of amylase and lipase elevation in COVID infection.

In addition, the rate of elevated amylase levels was 2.04 times higher in men than in women. In particular, hypotension (OR:6,63), sepsis (OR:6,20), ischemia related liver damage (OR:6,63) and renal failure (OR:5,18) were found to be significantly associated with pancreatic enzyme levels. (Table-3) There was a weak correlation between amylase level, age and gender in patients with Covid-19. Likewise, the presence of DM showed a weak but statistically significant correlation with the amylase level. The strongest correlation with the level of amylase was found to be related to the severity of Covid-19. Especially the presence of liver damage, renal failure, hypotension and MODS in these patients were correlated with amylase level. (Figure-1)

## DISCUSSION

We have been detected that 23% of patients with COVID-19 infection had pancreatic enzyme elevations. And there was a relationship between pancreatic enzyme elevation and severity of COVID-19 infection, hemodynamic instability and MODS.

Although 10,9% of patients with mild COVID-19 infection had elevated amylase, This rate was 34,9% in patients with severe COVID-19 infection. It has been detected that causes of pancreatic enzyme elevation were hypotension and ischemia in severe infection. Elevated amylase levels were 10,3% and 44,2% in patients with normal mean arterial pressure and with low arterial pressure (<60 mmHg) respectively. Out of 316 patients with a high level of amylase, 36.7% of patients recovered and 63.3% of patients died. 53% of patients with ischemic hepatitis had concurrently amylase and lipase elevations. And also next to liver and intestinal damage, pancreatic damage might occur in shock with the decreased blood flow to the gastrointestinal system.

In a study over the relation between COVID-19 infection and pancreas, it has been reported that pancreatic

damage was found 1-2% and 17% in patients with mild and severe infection consecutively. Additionally, it has been reported that pancreatic damage can be exacerbated with systemic inflammation. Amylase and lipase elevation, suggesting pancreatic damage, has been reported between 8.5%-17,3% in patients with COVID-19. Moreover, it has been stated that there were higher enzyme levels in severe patients.<sup>14-15-16-17</sup> Paralel to these studies, hemorrhagic and necrotic changes with focal pancreatitis were detected in one of the autopsy studies 5/11 (45,5%) and in the other study 2/8 (25%).

These changes without clinical signs have been attributed to ischemia and end-organ damage.<sup>18-19</sup> Therefore, it is quite difficult to use the elevated lipase and amylase developing in COVID-19 infection as a prognostic indicator. Since enzyme elevation occurs in the intensive care period where the disease is severe and requires mechanical ventilation. At this stage, most patients have single or multiple organ failure and receive vasopressor support. Therefore, the high amylase level is a result of the severity of COVID-19 infection.

As a result, although ACE-2 receptors are expressed highly in pancreatic tissue, pancreatic enzyme elevations occurring in COVID-19 infection might be result of severity of disease and hemodynamic instability. Otherwise, there would have been many pancreatitis caused by ACE-2 receptors. Despite over a hundred million cases, pancreatitis remained only at the level of case reports.<sup>20-21</sup>

### Conflict of interest

Regarding this study, the authors and/or their family members do not have scientific and medical committee membership or relationship with their members, consultancy, expertise, working status in any company, shareholding or similar situations that may have a potential conflict of interest.

### Financial Resource

During this study any support from any pharmaceutical company with a direct connection to the subject of the research or any company that supplies medical tools, equipments and materials, or any commercial company was not received. During the evaluation process of study, any material or intangible support that may adversely affect the decision to be made about study was not received.

### Author Contributions

**Idea/Concept:** FB; **Design:** NE, **Supervision/Consultancy:** BE, **Data collection and processing:** JK, **Analysis and Interpretation:** NE, **Literature Review:** JK, **Manuscript Writing:** FB-BE, **Critical Review:** FB, **Materials:** JK

### REFERENCES

1. Vedel AG, Holmgaard F, Rasmussen LS, Paulson OB, Thomsen C, Danielsen ER, Langkilde A, Goetze JP, Lange T, Ravn HB, Nilsson JC. Perfusion Pressure Cerebral Infarct (PPCI) trial - the importance of mean arterial pressure during cardiopulmonary bypass to prevent cerebral complications after cardiac surgery: study protocol for a randomised controlled trial. *Trials*. 2016 May 17;17(1):247
- 2 . Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *BioRxiv* 2020.
3. Furong Liu , Xin Long Bixiang Zhang ,Wanguang Zhang Xiaoping Chen , Zhanguo Zhang ,ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection *Clin Gastroenterol Hepatol* 2020 Aug;18(9):2128-2130.e2.
4. Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med* 2006;23(6):623–628.
5. Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*2010;47:193–199
6. James P. Corsetti, Christopher Cox, Thadeus J. Schlz, and Dean A. Arvan (1993). Combined Serum Amylase and Lipase Deteriminations for Diagnosis of Suspected. *CLIN CHEM*. 39/12, 2495-2499.

7. P. A. Banks, T. L. Bollen, C. Dervenis *et al.*, “Classification of acute pancreatitis 2012: revision of the Atlanta classification and definitions by international consensus,” *Gut*, vol.62, no.1 pp. 102–111, 2013.
8. Clinical management of COVID-19. WHO interim guidance. COVID-19: Clinical care. 2020. <https://www.who.int/publications/item/clinical-management-of-covid-19>.
9. Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut* 2004;53:1340–4.
10. Mofidi R, Duff MD, Wigmore SJ, et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *The British journal of surgery* 2006;93:738–44.
11. Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and Liver. *J Hepatol* 2020.
12. EASL. EASL clinical practice guidelines: drug-induced liver injury. *J Hepatol*. 2019;70:1222–611.
13. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int* 2008;73: 538–46
14. Bruno G, Fabrizio C, Santoro CR, Buccoliero GB. Pancreatic injury in the course of coronavirus disease 2019 (COVID-19): a not-so-rare occurrence. *J Med Virol* 2020.
15. McNabb-Baltar J, Jin DX, Grover AS, Redd WD, Zhou JC, Hathorn KE, et al. Lipase elevation in patients with COVID-19. *Am J Gastroenterol* 2020. <https://>
16. Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic injury patterns in patients with coronavirus disease 19 pneumonia. *Gastroenterology* 2020.
17. Barlass U, Williams B, Dhana K, Adnan D, Khan SR, Mahdavinia M, et al. Marked elevation of lipase in COVID-19 disease: a cohort study. *Clin Transl Gastroenterol* 2020;11:e00215.
18. Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. *Ann Intern Med* 2020.
19. Hanley B, Naresh KN, Roufousse C, Nicholson AG, Weir J, Cooke GS, et al. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. *Lancet Microbe* 2020.
20. Rabice SR, Altshuler PC, Bovet C, Sullivan C, Gagnon AJ. COVID-19 infection presenting as pancreatitis in a pregnant woman: a case report. *Case Rep Womens Health* 2020;27:e00228.
21. Cheung S, Delgado Fuentes A, Fetterman AD. Recurrent acute pancreatitis in a patient with COVID-19 infection. *Am J Case Rep* 2020;21:e9270

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