

ORIGINAL PAPER

Gastroenterology

Pancreatic damage in COVID-19: Why? How?

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Abstract

Object: We aimed to evaluate the elevation of amylase and lipase enzymes in coronavirus disease 2019 (COVID-19) patients and their relationship with the severity of COVID-19.

Method: In this study, 1378 patients with COVID-19 infection were included. Relation of elevated amylase and lipase levels and comorbidities with the severity of COVID-19 was analysed. The effects of haemodynamic parameters and organ failure on pancreatic enzymes and their relations with prognosis were statistically analysed.

Results: The 1378 patients comprised of 700 (51.8%) men and 678 (49.2%) women. Of all patients, 687 (49.9%) had mild and 691 (50.1%) patients had severe COVID-19 infection. Amylase elevation at different levels occurred in 316 (23%) out of 1378 patients. In these patients, the amylase levels increased one to three times in 261 and three times in 55 patients. Pancreatitis was detected in only six (1.89%) of these patients according to the Atlanta criteria. According to univariate and multivariate analyses, elevated amylase levels were significantly associated with the severity of COVID-19 (odds ratio [OR]: 4.37; $P < .001$). Moreover, diabetes mellitus (DM; OR: 1.82; $P = .001$), kidney failure (OR: 5.18; $P < .001$), liver damage (OR: 6.63; $P < .001$), hypotension (OR: 6.86; $P < .001$) and sepsis (OR: 6.20; $P = .008$) were found to be associated with mortality from COVID-19.

Conclusion: Elevated pancreatic enzyme levels in COVID-19 infections are related to the severity of COVID-19 infection and haemodynamic instability. In a similar way to other organs, the pancreas can be affected by severe COVID-19 infection.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection was initially considered to attack only the upper respiratory tract, but was later found to potentially affect almost all systems. This is caused by the angiotensin-converting enzyme 2 (ACE2) receptors that coronavirus binds to in order to enter the cells. These receptors are also commonly available in the gastrointestinal system such as in hepatic, pancreatic and colonic cells.^{1,2}

Recent studies have shown that COVID-19 infection can cause damage to the pancreas caused by the high expression of ACE2 receptors from the pancreatic tissue.³ Additionally, it has also been reported that hyperglycaemia can occur because of pancreatic islet cell damage in patients with COVID-19 and that severe patients

with COVID-19 should be followed up closely in terms of pancreatic damage.^{4,5}

In this study, we evaluated the amylase and lipase elevations in patients with COVID-19 in order to investigate the relationship between pancreatic enzyme elevations and the severity of COVID-19 infection and to identify the underlying conditions.

2 | PATIENTS AND METHODS

The study included 1378 patients with COVID-19 infection who presented to our hospital between March and December 2020. Clinical characteristics including temperature, blood pressure, laboratory parameters, treatments and comorbidities were monitored throughout

hospitalisation. In addition to other laboratory parameters, amylase and lipase levels were also studied in order to determine the ratio of patients with elevated pancreatic enzymes. Values above 105 U/L for amylase and 65 IU/L for lipase were considered high.⁶ Patients with pancreatitis were identified according to the Atlanta criteria.⁷

Additionally, pancreatic enzyme elevation in COVID-19 infection was investigated with regard to the severity of disease. Patients were divided into two groups based on the severity of their COVID-19 symptoms: mild ($n = 687$) and severe ($n = 691$). Patients with fever, headache, loss of taste and smell and generalised myalgia without tachypnoea (oxygen saturation $>92\%$) were considered to have a mild infection, whereas patients on invasive or non-invasive respiratory support or with deteriorated haemodynamic conditions were considered to have severe COVID-19 infection.⁸

The causes of pancreatic enzyme elevation were compared between patients with mild and severe COVID-19 infection and between surviving and non-surviving patients. Relation between elevated pancreatic enzymes and metabolic parameters, haemodynamic findings, single and multiple organ failures was also examined.^{9,10}

Hypotension was evaluated based on mean arterial pressure (MAP). A MAP value of 60-110 mmHg was accepted as normal, <60 mmHg as hypotensive and >110 mmHg as hypertensive.¹¹

Liver damage was determined according to the 2019 European Association for the Study of the Liver (EASL) guidelines, based on the upper limits of normal (ULN) serum alanine aminotransferase activity (ALT) and serum alkaline phosphatase activity (ALP), as follows: ALT $\geq 5 \times$ ULN or ALP ≥ 2 ULN [in the absence of known bone pathology] or ALT ≥ 3 ULN with simultaneous increase of total bilirubin concentration ≥ 2 ULN.¹² Kidney injury was determined according to the RIFLE (Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease) criteria.¹³

The study was conducted in accordance with the Helsinki Declaration and the study protocol was approved by the local ethics committee (No: 611, Date: 16 October 2020).

2.1 | Statistical analysis

Data were analysed using SPSS 26.0 for Windows (Armonk, NY: IBM Corp.). Normal distribution of data was assessed using Kolmogorov-Smirnov, Shapiro-Wilk test, coefficient of variation, skewness and kurtosis. Continuous variables were expressed as mean and standard deviation (SD), and categorical variables were expressed as percentages (%). 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 the significant results in groups. Welch's ANOVA and Kruskal-Wallis tests were performed for non-homogeneous parameters. Pearson and Spearman correlation coefficients were used to analyse the

What's known

- 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 pancreatic enzymes in COVID-19 patients.

What's new

- COVID-19 does not directly cause pancreatic damage.
- Pancreatic enzyme elevation in patients with COVID-19 develops in the advanced stages of the disease caused by multiple organ dysfunction and shock.

relationship between pancreatic enzyme elevation and other parameters. Univariate and multivariate analyses were performed to determine the factors associated with pancreatic enzyme elevation. All tests were bilateral and a *P*-value of $<.05$ was considered significant.

3 | RESULTS

The 1378 patients comprised of 700 (51.8%) men and 678 (49.2%) women. The prevalence of kidney failure, DM, ischaemic hepatitis and sepsis was significantly higher in patients with severe COVID-19 compared with patients with mild disease. Moreover, amylase and lipase levels were also higher in patients with severe COVID-19 (Table 1).

Amylase elevation at different levels occurred in 316 (23%) out of 1378 patients. In these patients, the amylase levels increased one to three times in 261 and three times in 55 patients. Pancreatitis was detected in only six (1.89%) of these patients according to the Atlanta criteria. Amylase and lipase elevation was found to be related to the severity of COVID-19 infection in the remaining patients. The development of DM, kidney failure, hypotension and ischaemic hepatitis was found to be related to mortality from COVID-19 infection. However, there was no relationship between lymphopenia and elevated amylase levels (Table 2). On the other hand, patients older than 65 years were more likely to have (1.89 times) elevated increased enzyme levels.

The prevalence of elevated amylase was 2.04 times higher in men than that in women. Hypotension (odds ratio [OR]: 6.63), sepsis (OR: 6.20), ischaemia-related liver damage (OR: 6.63) and renal failure (OR: 5.18) were found to be significantly associated with pancreatic enzyme levels (Table 3).

A very strong positive correlation was found between amylase and lipase levels in all patients ($r: .828, P < .001$), which implicates that the increased amylase in COVID-19 patients is caused by the pancreas. A weak correlation was found between amylase level and

TABLE 1 Demographic data and biochemical parameters of patients with mild and severe COVID-19

	Mild COVID-19±SD	Severe COVID-19±SD	P
N	687 (49.9%)	691 (50.1%)	
Age	60.2 (29-84)	65 (51-86)	<.001
Gender F/M	356/331	322/369	.053
Amylase (U/L)	82.6 ± 50.4	264.7 ± 292.0	<.001
Lipase (IU/L)	59.7 ± 51.2	79.0 ± 24.2	.045
ALT (IU/L)	70.4 ± 60.2	82.7 ± 56.4	<.001
AST (IU/L)	61.6 ± 40.7	180 ± 135.5	<.001
ALP (IU/L)	84.1 ± 35.4	133.2 ± 107.2	.295
GGT (IU/L)	54.2 ± 51.5	79.4 ± 58.9	.099
T.Bil (mg/dL)	0.67 ± 0.33	1.95 ± 1.53	<.001
LDH (IU/L)	411.9 ± 210	1137 ± 248.7	<.001
Urea (mg/dL)	45.7 ± 26.9	187.0 ± 92.8	<.001
Creatinine (mg/dL)	0.89 ± 0.49	3.74 ± 1.96	<.001
Glucose (mg/dL)	138 ± 85.0	290 ± 135	<.001
WBC (cell/μL)	9840 ± 4485	18 422 ± 6039	<.001
Lymphocyte (cell/μL)	1993 ± 665	1655 ± 946	<.001
CRP (mg/L)	107.8 ± 67.2	217.9 ± 69.1	<.001
Procalcitonin (ng/mL)	1.04 ± 4.65	8.03 ± 19.7	<.001

Abbreviations: ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; WBC, white blood cell; CRP, C reactive protein; ALT, alanine transaminase; AST, aspartate transaminase; LDH, lactate dehydrogenase; SD, standard deviation.

age or gender. Likewise, a weak but statistically significant correlation was found between amylase level and DM. A strong correlation was detected between the amylase level and the severity of COVID-19. Additionally, the presence of liver damage, renal failure, hypotension and multiple organ dysfunction syndrome (MODS) in these patients was moderately correlated with amylase level (Figure 1).

4 | DISCUSSION

We found that 23% of patients with COVID-19 infection had pancreatic enzyme elevations, and we also detected a relationship between pancreatic enzyme elevation and the severity of COVID-19 infection, haemodynamic instability and MODS.

Although 10.9% of patients with mild COVID-19 infection had elevated amylase levels, this rate was 34.9% in patients with severe COVID-19 infection. It was also revealed that the causes of pancreatic enzyme elevation were hypotension and ischaemia in patients with severe COVID-19 infection. Elevated amylase levels were detected in 10.3% and 44.2% of patients with a normal MAP and low MAP (<60 mmHg), respectively. Out of 316 patients with a high

amylase level, 36.7% of the patients recovered and 63.3% of them died. Moreover, 53% of patients with ischaemic hepatitis had both amylase and lipase elevations. We consider that after the development of shock in the body, pancreatic damage occurs in addition to hepatic and intestinal injury as a result of the decrease in blood flow to the gastrointestinal system.

A study investigating the relationship between COVID-19 infection and pancreas reported pancreatic damage in 1%-2% and 17% of patients with mild and severe infection, respectively. The authors suggested that pancreatic damage can be exacerbated by systemic inflammation.¹⁴⁻¹⁷ Amylase and lipase elevation suggestive of pancreatic damage has been reported in 8.5%-17.3% of patients with COVID-19. Moreover, higher enzyme levels have been reported in severe COVID-19 patients.¹⁴⁻¹⁷ Likewise, in two previous autopsy studies, five of 11 (45.5%) and two of eight (25%) cases were detected with focal pancreatitis with haemorrhagic and necrotic changes in the pancreas. These changes had no clinical manifestations and were attributed to ischaemia and end-organ damage.^{18,19} In the light of our data, we consider that pancreatic damage is the most important cause of amylase and lipase elevations. The exact pathophysiology of pancreatic damage remains unclear, while the most widely accepted hypothesis points to pancreatic ischaemia.²⁰⁻²² If septicaemia progresses towards septic shock, not only in COVID-19 but also in other infections, the resulting hypotension and vasodilation reduce blood flow to organs. To protect blood flow to vital organs such as the brain and heart, blood flow to the celiac, superior and inferior mesenteric arteries are reduced as a part of the protective mechanism. Afterwards, this is followed by renal and iliac arteries. This is the neurohormonal mechanism protecting vital organs. Gastrointestinal system is the target organ of shock and hypotension. As a result, the blood flow to the liver, pancreas and the entire gastrointestinal system is reduced, thereby causing symptoms such as nausea, vomiting, distension, ileus, or diseases such as ischaemic hepatitis.

Pancreas is supplied well by pancreatic arteries that stem from the splenic, gastroduodenal and superior mesenteric arteries. Amylase, lipase, aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) are released into the bloodstream caused by the ischaemia resulting from decreased blood flow to the pancreas.²³ This damage is mainly caused by haemodynamic deterioration, not by the virus itself. Similarly, in our study, elevated amylase and lipase levels were found to be associated with haemodynamic parameters and hypotension.

Although increased amylase and lipase levels might have clinical importance, it seems highly unlikely to use these parameters as prognostic indicators in clinical practice, mainly because enzyme elevation occurs during the intensive care period when the disease is severe and requires mechanical ventilation. At this stage, most patients have single or multiple organ failure and require vasopressor support.

In conclusion, although ACE2 receptors are expressed highly in pancreatic tissue, pancreatic enzyme elevations occurring in

TABLE 2 Relationship between amylase level in COVID-19 patients and gender, comorbid status, severity and consequence of COVID-19, haemodynamic status, other organ failures and laboratory parameters

Feature	Amylase (normal)	Amylase (1-3 times)	Amylase (more than 3 times)	P-values
N/%	1062 (77.0%)	261 (19.0%)	55 (4.0%)	
Gender				
Female (678%-49.2%)	565 (83.3%)	100 (14.8%)	13 (1.9%)	<.001
Male (700%-50.8%)	497 (71.0%)	161 (23.0%)	42 (6.0%)	
COVID-19 severity				
Mild COVID-19 (687%-49.9%)	612 (89.1%)	71 (10.3%)	4 (0.6%)	<.001
Severe COVID-19 (691%-50.1%)	450 (65.1%)	190 (27.5%)	51 (7.4%)	
COVID-19				
Healing (909%-66.0%)	793 (87.2%)	109 (12.0%)	7 (0.8%)	<.001
Death (469%-34.0%)	269 (57.4%)	152 (32.4%)	48 (10.2%)	
Diabetes				
Absent (866%-62.8%)	703 (81.2%)	143 (16.5%)	20 (2.3%)	<.001
Available (512%-32.6%)	359 (70.1%)	118 (23.0%)	35 (6.9%)	
Kidney failure				
Absent (934%-67.8%)	808 (86.5%)	114 (12.2%)	12 (1.3%)	<.001
AKI (316%-22.9%)	186 (58.8%)	101 (32.0%)	29 (9.2%)	
CRF (128%-9.3%)	68 (53.1%)	46 (36.0%)	14 (10.9%)	
Blood pressure				
Normal (810%-58.8%)	727 (89.7%)	76 (9.4%)	7 (0.9%)	<.001
Hypotension (466%-33.8%)	260 (55.8%)	161 (34.5%)	45 (9.7%)	
Hypertension (102%-7.4%)	75 (73.6%)	24 (23.5%)	3 (2.9%)	
ALT				
Normal (562%-40.8%)	488 (86.8%)	65 (11.6%)	9 (1.6%)	<.001
1-3 times (488%-35.4%)	389 (79.7%)	86 (17.6%)	13 (2.7%)	
3-5 times (135%-9.8%)	89 (65.9%)	37 (27.4%)	9 (6.7%)	
5-10 times (65%-4.7%)	36 (55.4%)	20 (30.8%)	9 (13.8%)	
>10 times (61%-4.4%)	32 (52.5%)	26 (42.6%)	3 (4.9%)	
>1000 (IU/L) (67%-4.9%)	28 (41.8%)	27 (40.3%)	12 (17.9%)	
AST				
Normal (468%-34.0%)	428 (91.4%)	36 (7.7%)	4 (0.9%)	<.001
1-3 times (564%-40.9%)	454 (80.5%)	98 (17.4%)	12 (2.1%)	
3-5 times (121%-8.8%)	76 (62.8%)	38 (31.4%)	7 (5.8%)	
5-10 times (71%-5.1%)	35 (49.3%)	27 (38.0%)	9 (12.7%)	
More than 10 times (45%-3.3%)	22 (48.9%)	16 (35.6%)	7 (15.5%)	
>1000 (IU/L) (109%-7.9%)	47 (43.1%)	46 (42.2%)	16 (14.7%)	
ALP				
Normal (966%-70.1%)	737 (76.3%)	191 (19.8%)	38 (3.9%)	.092
1-2 times (234%-17.0%)	176 (75.2%)	45 (19.2%)	13 (5.6%)	
More than 2 times (178%-12.9%)	149 (83.7%)	25 (14.0%)	4 (2.3%)	
GGT				
Normal (909%-66%)	722 (79.4%)	158 (7.4%)	29 (3.2%)	.072
1-2 times (254%-18.4%)	173 (68.1%)	62 (24.4%)	19 (7.5%)	
More than 2 times (215%-15.6%)	167 (77.7%)	41 (19.1%)	7 (3.2%)	

(Continues)

TABLE 2 (Continued)

Feature	Amylase (normal)	Amylase (1-3 times)	Amylase (more than 3 times)	P-values
Total Bilirubin				
Normal (1059%-76.9%)	860 (81.2%)	171 (16.2%)	28 (2.6%)	<.001
1-2 times (257%-18.6%)	172 (66.9%)	68 (26.4%)	17 (6.7%)	
More than 2 times (62%-4.5%)	30 (48.4%)	22 (35.5%)	10 (16.1%)	
LDH				
Normal (<225 IU/L) (161%-11.7%)	157 (97.5%)	4 (2.5%)	0 (0.0%)	<.001
Normal-1000 (IU/L) (969%-70.3%)	788 (81.3%)	158 (16.3%)	23 (2.4%)	
1000-2250 (IU/L) (148%-10.7%)	79 (53.4%)	55 (37.2%)	14 (9.4%)	
>2250 (IU/L)(100%-7.3%)	38 (38.0%)	44 (44.0%)	18 (18.0%)	
Lymphocyte levels				
Normal (724%-52.5%)	581 (80.3%)	119 (16.4%)	24 (3.3%)	.120
Mild lymphopenia (489%-35.5%)	360 (73.6%)	111 (22.7%)	18 (3.7%)	
Severe lymphopenia (165%-12.0%)	121 (73.3%)	31 (18.8%)	13 (7.9%)	

Abbreviations: AKI, Acute kidney injury; ALP, alkaline phosphatase, GGT, gamma glutamyl transpeptidase; ALT, alanine transaminase; AST, aspartate transaminase; CRF, Chronic renal failure; LDH, lactate dehydrogenase.

TABLE 3 Analysis of factors affecting enzyme elevation in COVID-19 patients with elevated amylase and lipase

Feature	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.89	1.46-2.44	.001	1.72	1.40-2.11	.001
Gender	2.04	1.57-2.64	.001	1.86	1.50-2.31	.001
COVID-19 Severity	4.37	3.28-5.81	<.001	3.76	2.90-4.88	<.001
Death from COVID-19	5.08	3.89-6.64	<.001	4.23	3.33-5.36	<.001
Diabetes	1.82	1.41-2.35	.001	1.72	1.40-2.11	.001
Kidney failure	5.18	3.95-6.79	<.001	3.78	3.00-4.75	<.001
Liver damage	6.63	4.56-9.64	<.001	3.09	2.43-3.94	<.001
Hypotension	6.86	4.50-10.40	<.001	5.67	3.90-8.22	<.001
Sepsis	6.20	3.83-10.05	.008	2.88	2.24-3.70	.003
Pancreatitis	21.2	2.54-166.7	.005	8.02	4.54-86.3	.026

COVID-19 infection might be associated with the severity of disease and haemodynamic instability. If the opposite was the case, we would have seen too many cases of pancreatitis, mainly because the pancreas has ACE2 receptors. As a matter of fact, despite the huge number of COVID-19 cases, which has exceeded 100 million, pancreatitis has remained only at the level of case reports.^{24,25}

DISCLOSURE

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.

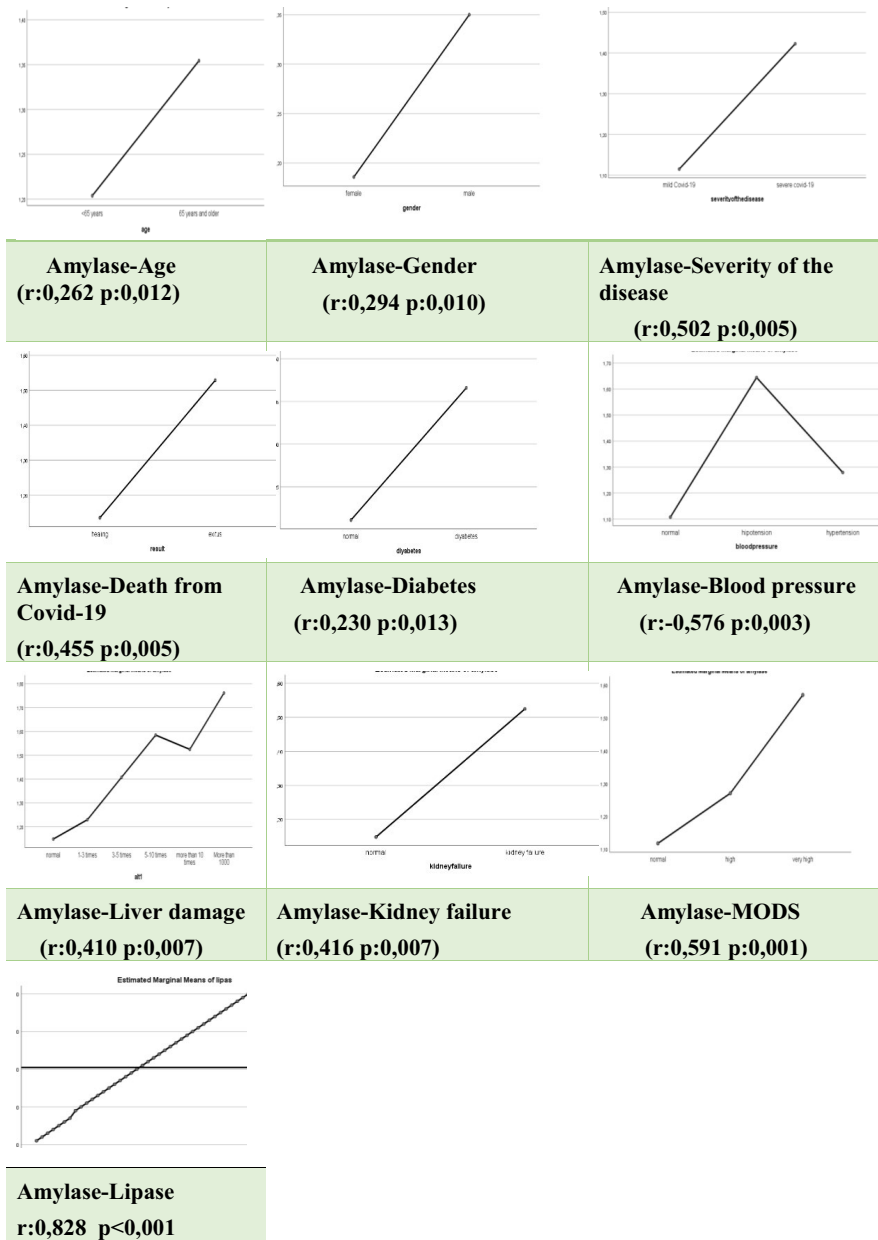


FIGURE 1 Correlation between amylase level and risk factors in COVID-19 patients with hyperamylasaemia

Pearson and Spearman correlation test was used. (r^* : correlation coefficient)

AUTHOR CONTRIBUTIONS

FB conceived of the ideas and conceptualised the study; NE designed the study and involved in analysis and interpretation of the results; BE involved in study supervision/consultancy; JK involved in data collection and processing, and in literature review; FB and BE wrote the manuscript; FB involved in critical revision of the manuscript; JK collected the materials.

DATA AVAILABILITY STATEMENT

Data may be made available upon request to the corresponding author.

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