Development of pancreatic injuries in the course of COVID-19

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Abstract

Background and study aims **: To investigate the clinical and laboratory characteristics of the cases with high lipase levels in the course of COVID-19.**

Patients and methods **: Hospital records of all cases, where lipase levels were measured, and the reverse transcriptase-polymerase chain reaction test due to SARS-CoV-2 was found positive, were retrospectively investigated. Of 127 COVID-19 patients tested for lipase, 20 (15.7%) had serum lipase levels above the upper laboratory limit. The patient group with the "high lipase level" was created from these subjects, and the rest constituted the "control" group.**

Results **: While body mass index (BMI) levels were higher in the high lipase group, (p=0.014), the number of those with pre-existing diabetes mellitus (DM) was also found higher in the high lipase group than the controls (p=0.002). The history of DM was detected to increase the risk of developing high lipase level 4.63 times higher. Only two patients were diagnosed with acute pancreatitis (AP). While oxygen saturations on admission (p=0.019) and discharge (p=0.011) were lower in the high lipase group than the controls, amylase (p<0.001), C-reactive protein (CRP) (p=0.002) and D-dimer (p=0.004) levels were found higher. In addition, more patients required the treatment in intensive care unit in the high lipase group, compared to the controls (p=0.027). Accordingly, time of hospital stay became also prolonged (p=0.003).**

Conclusions **: Pancreatic injuries or even AP may develop during SARS-CoV-2 infection, especially in those with pre-existing DM. Monitoring of pancreatic enzymes is important in COVID-19 patients, especially with pre-existing DM.** (Acta gastroenterol. belg., **2020**, 83, **585-592**).

Keywords : acute pancreatitis, COVID-19, pancreatic injury, SARS-CoV-2, viral pancreatitis.

Introduction

The incidence of coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become widespread and is threatening all humanity across the world (1). Although SARS-CoV-2 virus seems to be the pathogen affecting mainly the respiratory tract, heart and coagulation system, the fact that some patients experience some symptoms such as diarrhea, nausea, vomiting and abdominal pain suggests that the virus may lead to the involvement of the gastrointestinal system (GIS) and lead to serious disorders (2-5). As consistent with this information, the cases presenting with acute pancreatitis (AP) or the elevation of pancreatic enzymes in the course of SARS-CoV-2 infection have also been reported in literature with an increasing frequency despite the rarity of the cases (6-14). AP is the life-threatening inflammation of the pancreatic gland with a sudden-rapid onset. Although AP often develops due to the gallstones or heavy alcohol consumption, such factors as the viruses of coxsackie B and mumps are held responsible in approximately 10% of the cases with AP (15,16). COVID-19 due to SARS-CoV-2 is a new clinical condition, and there are no sufficient data about the pancreatic damage or injuries developing during the course of the disease. In the present study, the clinical and laboratory characteristics of the cases treated in our hospital due to the diagnosis of SARS-CoV-2-associated COVID-19 and presenting with pancreatic injuries during the follow-up period were scanned and examined retrospectively.

Methods

Our hospital is a tertiary facility and has been used as a center where COVID-19 patients are diagnosed and treated during the pandemic. During the period between 20th March 2020 and 9th June 2020, the cases where serum lipase levels were assayed with positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test and followed-up due to COVID-19 were included into the analysis. The present study was retrospectively designed as a cohort study, and an approval was obtained from the local ethics committee of the university. In our hospital, a total of 559 patients were diagnosed with SARS-CoV-2 positivity through RT-PCR test during the study period. Of 559 patients, however, 31 died, and the rest were sent home for contact tracing after receiving the standard treatment in the hospital. From the

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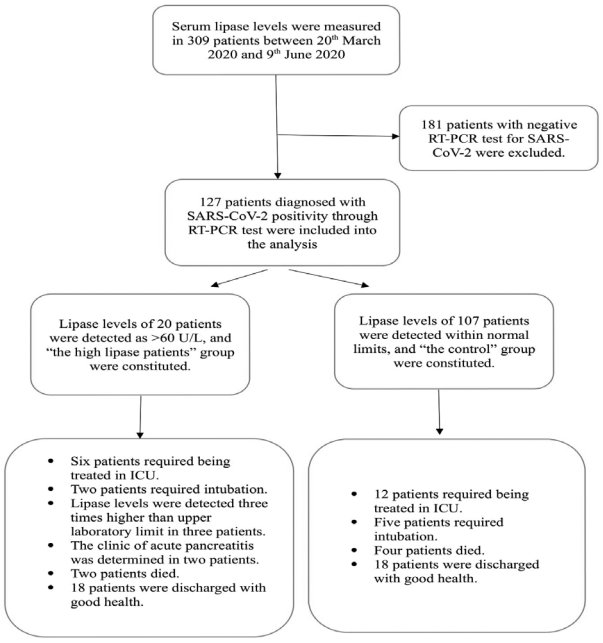

Figure 1. — COHORT diagram of study population. RT-PCR : Reverse transcriptase-polymerase chain reaction, SARS-CoV-2 : Severe acute respiratory syndrome coronavirus-2, ICU : Intensive care unit.

hospital automation system, a total of 430 lipase tests were performed for 309 patients during the study period, and 127 were found to have RT-PCR test positivity for SARS-CoV-2. The COHORT diagram is presented in Figure 1. During the study period, routine biochemical tests, including the measurements of amylase and lipase levels, were performed using a device of Architect c 8000 model (Abbott Diagnostic, Lake Forest, IL, USA). While lipase levels were measured by the spectrophotometric method using quinone staining, amylase levels were measured by the spectrophotometric method using 2-chlorine 4 nitrophenol substrate. In our laboratory, the reference limits for amylase and lipase were 25-125 U/L and 13-60 U/L, respectively. One hundred and twenty-seven cases underwent RT-PCR test and were found to have SARS-CoV-2 positivity. For 127 patients, lipase levels were also measured during the course of COVID-19, and 20 were found to have higher lipase levels above the laboratory limit (>60 U/L). Therefore, the patient group with "high lipase level" was created from these cases. Even so, the "control" group was contituted from the remaining 107 patients with normal lipase levels (Figure 1). Patients' symptoms on admission, pre-existing diseases, various examination findings, hemogram and biochemical tests on admission, results of control amylase and lipase tests (if repeated), and imaging methods were scanned from the automation system and recorded on the patients' charts. The low-dose thorax computerized tomography (CT) device (TOSHIBA Aquilion 16 CT Scanner in Kyoto, Japan) for imaging COVID-19 patients and the 1.5T magnetic resonance imaging (MRI) scanner (Siemens Magnetom Aera, Erlangen, Germany) for AP were utilized during the study. AP was diagnosed based on the Atlanta criteria, and the patients having at least two of the three criteria were diagnosed with AP (17).

Statistical analyses

The normality analyses of the data were performed using the Kolmogorov-Smirnov or the Shapiro-Wilk tests. In group comparisons, the student *t*-test was used for continuous variables with normal distribution, and the Mann-Whitney-U test was utilized for non-normally distributed variables. In the comparisons of the paired groups for discrete variables, the Fisher's exact test was used, while the Pearson chi-square test was used for the comparisons of the groups more than two. The continuous variables with normal distributions were given as mean±standard deviation (SD), while the continuous variables not showing normal distribution were given as median (min : max). In the modeling of categorical dependent variables, the binary regression analysis was used. The statistical significance of the results was evaluated at 95% confidence interval (CI), and a $p \leq 0.05$ was considered to be significant.

Results

Twenty (15.7%) of 127 COVID-19 patients diagnosed with SARS-CoV-2 RT-PCR test positivity at least once were observed to have higher serum lipase levels above the laboratory limits, and so these patients were enrolled into the study as the "high lipase level" group. Compared to the controls, the levels of body mass index (BMI) were found higher in the "high lipase level" group as 30.7±4.6 kg/m^2 *vs* 27.8±4.5 kg/m^2 (p=0.014), and as expected, the lipase levels were also determined to be higher in the "high lipase level" group, compared to the controls [91.0 (65:451) U/L *vs* 31 (9:86) U/L, respectively, (p<0.001)]. Additionally, the number of the patients with pre-existing diabetes mellitus (DM) was found higher in the "high lipase level" group [10 (50%)] than the "controls" [19 (17.8%), respectively (p=0.002)]. Of the patients with DM, 11 received the dipeptitdyl peptidase-4 (DDP-IV) inhibitor treatment, and of these 11 DM patients, four (36.3%) were in the "high lipase level" group, while seven (36.7%) were in the "control" group (p=0.868). While six (33.3%) of 18 patients receiving no DPP-IV inhibitor treatment were in the "high lipase level" group, 12 (66.7%) were in the control group (p=0.868), and no difference was detected between the groups in terms of the number of the patients with the history of hypertension (HT), coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD). While anorexia was observed only in one patient in the high lipase group (p=0.002), the number of asymptomatic patients was similar in both groups. No difference was also found between both groups in terms of other symptoms. The data related to the issues are presented in Table 1. Although the lipase levels of three patients among 20 patients in the "high lipase level" group were

Table 1. — **Some clinical and demographic characteristics in high lipase level and control groups**

	High Lipase Level Group (n=20)	Control Group (n=107)	p
Age	55.5±18.9*	51.2±16.7	0.276
Gender (F/M)	(9/11)	(45/62)	0.807
BMI	30.7±4.6	27.8±4.5	0.014
History of DM [n/(%)]	10/(50)	19/(17.8)	0.002
DPP-IV inhibitor [Yes/No(%/%)]	4/6(40/60)	7/12(36.8/63.2)	0.868
History of HT [n/(%)]	4/(20)	17/(15.9)	0.650
History of CAD [n/(%)]	1/(5)	7/(6.5)	0.794
History of COPD [n/(%)]	1/(5)	7/(6.5)	0.794
Fever [n/(%)]	5/(25)	34/(31.8)	0.547
Cough [n/(%)]	5/(40)	43/(40.2)	0.988
Dyspnea [n/(%)]	4/(20)	15/(14)	0.491
Nausea [n/(%)]	1/(5)	4/(3.7)	0.790
Vomiting [n/(%)]	1/(5)	3/(2.8)	0.606
Anorexia [n/(%)]	1/(5)	0/(0)	0.002
Diarrhea [n/(%)]	0	2/(1.9)	0.538
Abdominal pain [n/(%)]	2/(10)	3/(2.8)	0.176
Headache [n/(%)]	1/(5)	10/(9.3)	0.526
Sore throat [n/(%)]	2/(10)	12/(11.2)	0.873
Anosmia [n/(%)]	0/(0)	9/(8.3)	0.178
Muscle pain [n/(%)]	2/(10)	13/(12.1)	0.785
Fatigue [n/(%)]	5/(25)	29/(27.1)	0.845
Asymptomatic [n/(%)]	4(20)	21(19.6)	0.910
Chloroquine treatment [n/(%)]	20/(100)	106/(99.1)	0.664
Azithromycin treatment [n/(%)]	18/(90)	97(90.7)	0.927
Favipiravir treatment [n/(%)]	12/(60)	29/(27.1)	0.004
LMWH treatment [n/(%)]	20/(100)	98/(91.6)	0.178
Broad-spectrum treatment [n/(%)]	12/(60)	31/(29)	0.007
Oseltamivir treatment [n/(%)]	13/(65)	77/(72)	0.529
Tocilizumab treatment [n/(%)]	5/(25)	5/(4.7)	0.002
Convalescent plasma treatment [n/(%)]	1/(5)	1/(0.9)	0.180
Requirement for ICU [n/(%)]	6(30)	12 (11.2)	0.027
NIMV [n/(%)]	3(15)	5(4.7)	0.112
Intubation [n/(%)]	2(10)	5(4.7)	0.338
Outcome (Exitus letalis) [n/(%)]	2/(10)	4/(3.7)	0.226

BMI : Body mass index, CAD : coronary artery disease, COPD : Chronic obstructive pulmonary disease, DM : Diabetes mellitus, DPP-IV : Dipeptitdyl peptidase-4, HT : Hypertension, ICU : Intensive care unit, LMWH : Low molecule-weighted heparine, NIMV : Non-invasive mechanic ventilation. *Parametric data were given as mean±standard deviation (SD), and non-parametric data were presented as median (min-max).

detected to be three times higher than the upper laboratory limit, only two met the diagnostic criteria of AP under the Atlanta Classification criteria. Of these two patients, the first was a 70-year-old male patient presenting with the complaints of abdominal pain and fatigue without the history of alcohol consumption and gallstones. This patient with BMI of 29.4 kg/m^2 was seen to have diffuse patchy ground-glass opacity (GGO) shadows in both lung parenchymas on low-dose thorax CT scan, and the amylase and lipase levels were measured as 331 U/L and 293 U/L, respectively. Diffusion restrictions were detected in the pancreas on conventional pancreatic and diffusion MRI (Figure 2). Then, the patient was considered to have AP, and so treated in intensive care unit (ICU). Within the follow-up period, the lipase levels were observed to return to normal limits, and the patient was discharged from the hospital in good health. However, the other patient was a 47-year-old obese woman with the history of DM and on use of insulin, and had BMI of 38.3 kg/m^2. On admission, the patient was detected to have flu-like complaints for the last 3 days and nausea for the last day. Thorax low-dose CT scan revealed bilateral, predominantly subpleural-localized GGO images, seen more commonly in the middle and lower lung zones. The patient having no history of alcohol consumption, gallstones and abdominal pain underwent some tests due to nausea, and when the serum amylase and lipase levels were found as 175 U/L and 451 U/L respectively, the conventional and diffusion MRI was performed, and so showing diffusion restriction in the tail region of the pancreas. Therefore, the patient was considered AP and treated in ICU. Another patient having lipase levels of three times higher than the upper laboratory limit was a 81-year-old female with the history of CAD and BMI of 27.6 kg / m2. When the general condition was impaired and hypoxia developed, the patient had been

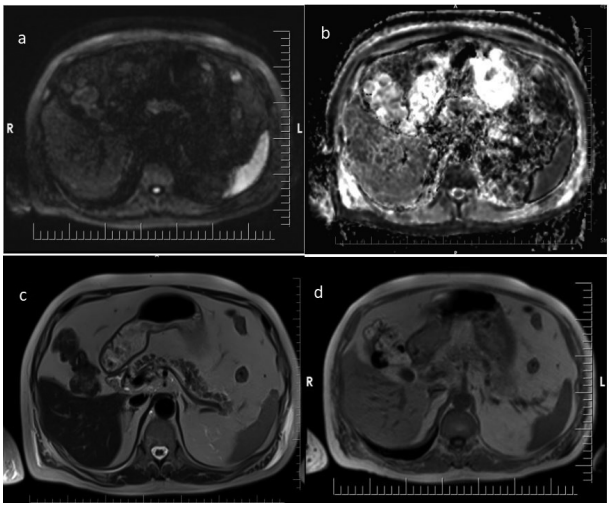

Figure 2. — Magnetic resonance imaging (MRI) findings of the pancreas in the overweight patient diagnosed with acute pancreatitis a) An increase of signals showing restricted diffusion in the head and body of the pancreas on diffusion-weighted MR images, b) Signal loss showing restricted diffusion in the head and body of the pancreas head-body on the apparent diffusion coefficient (ADC) map of diffusion-weighted MR imaging, c) Normal-looking pancreatic tissue signal on T2-weighted MRI and d) Normal pancreatic tissue signal on in-phase images.

taken to ICU, and non-invasive mechanical ventilation (NIVM) had been performed. During the follow-up, the patient was taken to the service from ICU after the clinical improvement, and the serum lipase level was found to be 246 U/L. However, because the patient had no symptoms such as abdominal pain, nausea and vomiting, pancreas imaging was not performed, and the lipase level decreased by 38 U/L within 8-day follow-up period. However, the patient developed hypoxia again in the following days. NIVM was performed first, and due to the deterioration in the general condition, the patient required for mechanical ventilation. So the treatment was continued in ICU. However, the patient died on the 41st day of hospitalization.

Considering the medications used in the treatment, even more patients in the "high lipase level" group were seen to receive favipiravir, tocilizumab and broad-spectrum antibiotic treatment (Table 1).

While O_2 saturation levels were lower on admission (p=0.019) and on discharge (p=0.011) in the "high lipase level" group compared to the controls, the levels of creatinine (p=0.010), amylase (p<0.001), C-reactive protein (CRP) (p=0.002) and D-dimer (p=0.004) were found higher. In addition, the time of hospital stay was also longer in the "high lipase levels" group, compared to the controls (p=0.003) (Table 2).

When the logistic regression analysis was performed, while age, glucose and creatinine levels were determined as the factors requiring the hospitalization in ICU, age was found as the only determining factor on mortality. In addition, the risk of developing increased lipase levels was determined as 4.63 times higher in those with the history of DM (p=0.003) (Table 3).

Thorax CT involvements were similar in the high lipase and the control groups. In the high lipase group, six (30%) patients required hospitalization in ICU, and of these six patients, three (15%) underwent NIVM, while two (10%) patients were intubated. Even so, among the controls, 12 patients (11.1%) were found to be hospitalized in ICU. Both NIMV and intubation were performed for five (4.7%) of 12 patients hospitalized in ICU. There was no difference between the "high lipase level" and

Table 2. — **Laboratory characteristics of high lipase level and control groups**

	High Lipase Level Group (n=20)	**Control Group (n=107)**	**p**
Saturation on admission	93.5(87:99)	96(80:99)	0.019
Glucose	124.0(86:403)	113.0(78:463)	0.193
Creatinin	1.09(0.53:14.3)	0.89(0.59:5.78)	0.010
ALT (0-55 U/L)	31.5(10:97)	27.0(9:186)	0.321
AST (5-34 U/L)	31.5(15:83)	25.0(13:96)	0.088
Total Bilirubin (0-1 mg/dL)	0.5(0.2:0.9)	0.4(0-3.5)	0.466
Direct Bilirubin (0-0.5 mg/dL)	0.2(0.1:0.4)	0.2(0.0:0.8)	0.228
LDH (125-243 U/L)	263.0(179.0:475.0)	219.0(89.0:615.0)	0.054
GGT (9-36 IU/L)	41(13:93)	25.5(8:212)	0.068
Amylase (25-125 U/L)	90.5(53:331)	64.0(19:120)	<0.001
Lipase (13-60 U/L)	91.0(65:451)	31.0(9:86)	<0.001
CRP (0.1-5 mg/L)	110.8(3:297.6)	42.2(0.1:343.4)	0.002
D-Dimer (0-550 ng/mL)	1584.0(369.9:4381.0)	721.0(170.7:4381.0)	0.004
Leukocyte	5775.0(4130.0:12910.0)	5350.0(1230.0:19250.0)	0.713
Neutrophil count	4190.0±2310.5*	4046±2552.9	0.713
Percentage of Neutrophil	65.5(46.9:87.4)	63.2(32.3:95.6)	0.704
Lymphocyte count	1573.5±561.6	1516.5±658	0.580
Percentage of lymphocytes	27.9±11.9	28.0±12.8	0.864
Saturation on discharge	94(81:98)	96(86:99)	0.011
Hospitalization time	11.5(3:41)	8(0:38)	0.003

ALT : Alanine aminotranspherase, AST : Aspartate aminotranspherase, CRP : C-reactive proteine, GGT : Gamma glutamil transpherase, LDH : lactate dehydrogenase. *Parametric data were given as mean±standard deviation (SD), and non-parametric data were presented as median (min : max).

Table 3. — **Modeling of Logistic regression**
ODDS = 1.126*exp (age)+1.012*exp (glucose)+1.454*exp (creatinine) (1)
ODDS = 1.123*exp (age) (2)
ODDS = 0.114+4.632*exp (pre-existing DM) (3)
Models 1, 2 and 3 are modeling the variables of the hospitalization in ICU, the mortality rate and the inclusion in the high lipase level group.

Model Number	**-2 Log Likelihood**		**Cox & Snell R Square**			**Nagelkerke R Square**		
1	65.476		0.260			0.465		
2	34.559		0.103			0.325		
3	101.953		0.066			0.113		
Model 1. Hospitalization in ICU								
	B	S.E.	Wald	df	Sig.	Exp(B)	95% (CI) for EXP(B)	
							Lower	Upper
Age	.119	.032	14.061	1	.000	1.126	1.058	1.198
Glucose	.011	.004	9.096	1	.003	1.012	1.004	1.019
Creatinine	.374	.163	5.248	1	.022	1.454	1.056	2.003
Constant	-11.466	2.598	19.477	1	.000	.000		
Model 2. Mortality								
	B	S.E.	Wald	df	Sig.	Exp (B)	95% (CI) for EXP(B)	
							Lower	Upper
Age	.116	.039	8.888	1	.003	1.123	1.041	1.213
Constant	-10.463	2.863	13.359	1	.000	.000		
Model 3. Inclusion in the high lipase level group.								
	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Preexisting DM	1.533	.514	8.901	1	.003	4.632	1.692	12.679
Constant	-2.175	.334	42.469	1	.000	.114		

DM : Diabetes mellitus

"control" groups in terms of the frequency of those undergoing NIMV and intubation (p=0.112 and p=0.338, respectively). When both groups were compared in terms of hospitalization in ICU, more patients in the high lipase group were observed to require the treatment in ICU, compared to the controls (p=0.027). While two (10%) of 20 patients in the "high lipase level" group died, four (3.7%) individuals passed away in the "control" group consisting of 107 subjects (p=0.226).

When the correlation analysis was performed, it was seen that there was a negative correlation between lipase and O_2 saturations on admission (r=-0.206, p=0.036) and discharge (r=-0.241, p=0.015), and a positive correlation between lipase and amylase (r=0.702, p<0.001), CRP (r=0.217, p=0.014), D-dimer (r=0.229, p=0.011) and hospitalization time (r=0.260, p=0.003).

Discussion

In the present study, lipase levels were found higher than the upper laboratory limit in approximately 15.7% of the patients whose lipase levels were measured due to SARS-CoV-2 infection. It was also detected that of the patients, only two displayed the precise clinic of AP, and that when compared with the controls, more patients had pre-existing DM and higher BMI in the "high lipase level" group. Besides, while O_2 saturation levels on admision and discharge were lower, the levels of creatinine, amylase, CRP and D-dimer were also observed to be higher in the "high lipase level" group than those of the "control" group. In our study, however, it was determined that in the "high lipase level" group, the hospitalization time was longer, and the rate of those hospitalized in ICU was higher than that of the "controls". However, the rate of asymptomatic patients was similar in both groups. Although most of the patients experiencing COVID-19 due to SARS-CoV-2 are asymptomatic, the disease progresses severely in approximately 10-20% of the patients. Much as such clinical conditions as pneumonia and myocarditis are frequently reported in the course of COVID-19, the cases with AP have recently been reported as an accompanying disease with SARS-CoV-2 infection (6,7,9-14). Since SARS-CoV-2 infection originates from a novel and unknown type of virus, it was detected in our hospital that many physicians started to keep the content of the tests wide enough to include the measurements such as amylase and lipase levels, even when the cases exhibited no symptoms suggesting the pancreatic pathologies. Although AP is a potentially fatal condition and often develops due to alcohol consumption or gallstones, such factors as obesity, hypercalcemia, hypertriglyceridemia, use of medications and viruses also play a role in its etiology (15,16,18). It is known that the risk of AP increases slightly in the patients with DM (19,20), and the presence of pre-existing DM increases significantly the risk of mortality in those presenting with AP (21). The drugs used in the treatment of diabetic patients or concomitant hypertriglyceridemia may also increase the risk of developing AP in diabetic population (22). None of our patients in the "high lipase level"

group had any known biliary tract problems or other clinical factors to cause the risk of AP, such as alcohol consumption, hypercalcemia or hypertriglyceridemia, but higher BMI levels and more diabetic patients were detected in the this group. In regulating the blood glucose levels of diabetic patients treated in our hospital due to COVID-19, we tried to regulate glucose levels with insulin treatment as much as possible. Although lipase levels were three times higher than the upper laboratory limit in three patients in the "high lipase level" group, only two met the diagnostic criteria of AP under the Atlanta Classification criteria (17). One of these two patients was overweight, and the other was obese. While the overweight patient had typical abdominal pain, there was the complaint of nausea in the other. Although both patients diagnosed with AP had pneumonia, there was neither fever nor cough in the patients. In the patient with obesity, flu-like symptoms were also detected. In the overweight patient, however, although there was no shortness of breath at initial diagnosis, O_2 saturation was seen to decrease in the follow-ups, and so O_2 treatment was administered. Of both patients developing the clinic of AP, while the highest amylase and lipase levels were detected to be 2.7 times (day 1) and 4.9 times (day 14) higher above the normal limits respectively in the overweight patient, the highest levels of amylase and lipase were 1.4 times (day 1) and 7.52 times (day 1) higher in the obese patient respectively, and restricted diffusion areas were observed on pancreatic MR images of both cases. Therefore, both patients were admitted and treated in ICU, but required neither intubation nor NIMV. The other patient whose lipase level was three times higher than the upper laboratory limit but not meeting the AP diagnostic criteria was overweight and had the history of CAD. The patient initially followed-up in ICU and undergoing NIVM was taken to the service upon the improvement of general condition. Since there was no clinic of pancreatitis, no pancreas imaging had been performed in the patient with high lipase levels. When the patient, whose lipase level had returned to normal, developed hypoxia again NIVM was performed first ; however, since the general condition was deteriorated, the patient required for the mechanical ventilation, and the treatment was continued in ICU. Unfortunately, the patient died on 41st hospitalization day.

In our study, pre-existing DM was determined in more patients in the "high lipase level" group. In addition, when the logistic regression analysis was performed, the risk of elevated lipase levels was also found to increase 4.63 times in the presence of pre-existing DM. There is a risk of developing AP after the administration of incretin-based treatments, such as the glucagona-like peptide-1 (GLP-1) analogue and DPP-IV inhibitors. In our study, none of the patients had previously received GLP-1 analogue although there were some patients previously receiving DPP-IV inhibitors, and the frequency of those receiving DPP-IV inhibitors was also similar in both groups. To the best of our knowledge, the fact that more patients with pre-existing DM were in the "high lipase level" group, and the risk of detecting the elevation of lipase level in the presence of DM increased 4.63 times upon the regression analysis are novel findings, because we found no evidence or information related to the issue in literature. Considering that DM itself increases the risk of developing AP, and the risk of mortality also increases in the presence of DM (20,21,23), the patients with SARS-CoV-2 infection, especially having pre-existing DM may require being followed-up closely in terms of the development of AP or pancreatic pathology. COVID-19 is known to be more lethal in the elderly, and the risk of becoming symptomatic is likely to increase among the elderly (24,25). It is also known that the risk of hospitalization in ICU is increased in case of hyperglycemia (25) and renal failure (26). As consistent with these data, it was determined in our study that an increase was observed in the need for hospitalization in ICU and the risk of mortality as the age advanced, and the risk of requiring the care in ICU increased in case of high blood sugar and high creatinine. One of the largest studies investigating the issue in those with SARS-CoV-2 infection was conducted by Wang et al., and it was reported in the study that nine (17%) of 52 patients with COVID-19 pneumonia exhibited pancreatic damages defined by the elevation of amylase and lipase levels, the average age was 55 (25-71 years), the most common complaints on admission were fever and respiratory symptoms, and the clinical symptoms were subtle or mild in terms of pancreatitis. In the same study, it was also stated that while five patients had other underlying concomitant diseases such as HT, DM and heart disease, and a total of four patients were in the serious disease category, those in the serious disease category showed decreases in lymphocyte and lymphocyte subgroup counts, but an increase was seen in liver, myocardial enzymes and inflammatory cytokines (10). When the study by Wang et al. was examined, amylase and lipase levels were seen not to be twice higher than the upper laboratory limit in any of the study participants, and since Wang et al. even reported the upper reference limit of lipase level as 70 U/L, only four patients were detected to exceed this value (124, 112, 83 and 77 U/L). In addition, in the study by Wang et al., we neither found the clinical data suggesting the diagnosis of AP such as abdominal pain under the Atlanta criteria, nor saw at least three times higher elevation of the enzymes or the data showing the pancreatic damage on pancreatic CT or MRI. In the cohort study where the retrospective analysis of 71 COVID-19 patients with SARS-CoV-2 mRNA positivity was assessed by McNabb-Baltar et al., it was stated that lipase levels were above the normal limit in nine patients, only two of whom had threefold higher lipase levels or more, the cases had no clinic of AP, and the elevation in lipase levels was not associated with the poor outcome and symptoms (14). In the study performed by Liu et al., while both amylase and lipase levels were found to be elevated in only one (1.85%) of 54 patients with mild

COVID-19, the researchers reported the increased levels of amylase in 12 (17.91%) and of lipase in 11 (16.41%) patients with severe COVID-19. Among only five (7.46%) patients developing the elevation of pancreatic enzymes in severe COVID-19 patients group, the focal enlargement of the pancreas or the dilatation in the ducts was reported to be seen on CT (24). In our study, both of the lipase and amylase levels were also higher above the upper laboratory limit in our patients In addition, the levels we determined were also far higher than those stated by Wang et al. Only two of 20 patients with elevated levels of lipase met the diagnostic criteria of AP under the revised Atlanta classification criteria. Although the frequency of the patients undergoing NIMV and intubation was similar in our study, O_2 saturation levels on admission and discharge were detected to be lower in the high lipase group compared to the controls. However, the parameters indicating the severity of inflammation and disease, such as CRP and D-dimer, were determined to be higher, and more patients in the "high lipase level" group required the hospitalization in ICU, but there was no difference between the groups in terms of mortality rates. In our study, pancreatic MRI was found out to be performed only for two of 20 patients in the high lipase group and to be compatible with pancreatitis. The fact that lipase levels were not too high or clinical in other patients may have caused pancreatic CT or MRI not to be performed. Considering that Liu et al. reported there were pathologies in the pancreatic images in 7.46% of those with severe COVID-19 (24), the fact that pancreatic CT or MRI was not performed in too many patients in our study may have caused many cases to be ignored, and such a condition is one of the limitations in our study.

In recent studies, it has been reported that approximately 50% of COVID-19 patients have SARS-CoV-2 mRNA in stool specimens, and 18% of the cases have GIS symptoms (25). Schepis et al. showed SARS-COV-2 mRNA in cyst fluid in a patient presenting with AP and also associated pancreatic pseudocyst during the course of COVID 19 pneumonia (26). Although its mechanism still remains fully unknown, cytopathic effects of the virus or systemic inflammation and immune mediated mechanisms, as well as the medications used, may cause pancreatic damages and enzymatic elevation in the patients with SARS-CoV-2 (27). In addition, the widespread expression of the ACE-2 receptors in pancreatic islet cells may cause the development of pancreatic pathology and DM, or impaired glycemic control in those with SARS-CoV-2 (24).

As the limitations in our study, while many physicians performed tests to measure pancreatic enzymes such as lipase and amylase, whether the cases had the symptoms suggesting the pancreatic pathology, in the follow-up of those with SARS-CoV-2 positivity through PCR tests, others performed no tests to measure such enzymes since SARS CoV2 was a new virus and was not well-known by physicians. That lipase and amylase levels were not measured in each patient, and that the measurement of these enzymes was dependent on the physician's request rather than the symptoms in the patients were also the limitations in our study. In addition, the fact that our study was retrospective, such enzymes as amylase and lipase were not studied collectively, systematic or periodic monitoring of these enzymes was not performed on a routinely basis in most of the patients with slightly elevated enzyme levels, and as mentioned in above paragraphs, CT and MRI were not performed in each patient with elevated pancreatic enzyme can be considered other limitations in our study.

In conclusion, the available data show that SARS-CoV-2 infection may have effects on the pancreas, as well as the lungs and heart. The risk of developing elevated pancreatic enzymes is high in the patients with SARS-CoV-2 infection, especially in those with pre-existing DM. Again, due to such factors as low saturation levels in the patients with high lipase levels, the increase in the parameters such as CRP and D-dimer indicating the inflammation and disease severity, and also the higher frequency of hospitalization in ICU, the determination of pancreatic enzyme levels may be used as an indicator of disease activity and prognosis in the patients with SARS-CoV-2 infection. In addition, such an indicator can also be inserted into the routine practice in the follow-up of such patients. However, in the patients with SARS-CoV-2 infection, the frequency of pancreatic damage and the clinical importance of elevated amylase or lipase levels due to the pancreatic damage have yet to be elucidated fully. In order to detect the possible development of a pancreatic pathology earlier, pancreatic enzymes should be followed-up in case of the slightest suspicion in those with SARS-CoV-2 infection, even if there are no typical clinical symptoms. We consider that further comprehensive studies are required to elucidate and support the entity.

Conflict of interests

Authors declares no conflict of interests.

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References

1. AHN DG, SHIN HJ, KIM MH, LEE S, KIM HS, MYOUNG J *et al.* Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). *J Microbiol Biotechnol*., 2020, **30** : 313-324.
2. SINONQUEL P, AERTS M, BADAOUI A, BISSCHOPS R, BLERO D, DEMEDTS I *et al.* BSGIE survey on COVID-19 and gastrointestinal endoscopy in Belgium : results and recommendations. *Acta Gastroenterol Belg*., 2020, **83** : 344-354.
3. DAHLQVIST G, CICCARELLI O, VAN VLIERBERGHE H, BERREVOET F, VANWOLLEGHEM T, YSEBAERT D *et al.* Liver transplantation during the COVID-19 epidemic : recommendations from the Belgian Liver Intestine Transplant Committee (BeLIAC). *Acta Gastroenterol Belg*., 2020, **83** : 340-343.
4. MOREELS TG. COVID-19 and gastrointestinal endoscopy in Belgium : uncertainty and ambiguity. *Acta Gastroenterol Belg*., 2020, **83** : 337-338.

5. MEROLA E. Prevalence of liver injury in patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Acta Gastroenterol Belg*., 2020, **83** : 454-460.
6. ALOYSIUS MM, THATTI A, GUPTA A, SHARMA N, BANSAL P, GOYAL H. COVID-19 presenting as acute pancreatitis. *Pancreatology*, 2020, **20** : 1026-1027.
7. ANAND ER, MAJOR C, PICKERING O, NELSON M. Acute pancreatitis in a COVID-19 patient. *Br J Surg*., 2020, **107** : e182.
8. 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! *Gastroenterology*, 2020. in press.
9. HADI A, WERGE M, KRISTIANSEN KT, PEDERSEN UG, KARSTENSEN JG, NOVOVIC S *et al.* Coronavirus Disease-19 (COVID-19) associated with severe acute pancreatitis: Case report on three family members. *Pancreatology*, 2020, **20** : 665-667.
10. WANG F, WANG H, FAN J, ZHANG Y, WANG H, ZHAO Q. Pancreatic Injury Patterns in Patients With Coronavirus Disease 19 Pneumonia. *Gastroenterology*, 2020, **159** : 367-370.
11. MEIRELES PA, BESSA F, GASPAR P, PARREIRA I, SILVA VD, MOTA C *et al.* Acalculous Acute Pancreatitis in a COVID-19 Patient. *Eur J Case Rep Intern Med*., 2020, **7** : 001710.
12. BOKHARI S, MAHMOOD F. Case Report: Novel Coronavirus-A Potential Cause of Acute Pancreatitis? *Am J Trop Med Hyg*., 2020. in press.
13. 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). in press
14. 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, **115** : 1286-1288.
15. RAWLA P, BANDARU SS, VELLIPURAM AR. Review of Infectious Etiology of Acute Pancreatitis. *Gastroenterology Res*., 2017, **10** : 153-158.
16. CAPPELL MS. Acute pancreatitis: etiology, clinical presentation, diagnosis, and therapy. *Med Clin North Am*. 2008, **92** : 889-923, ix-x.
17. BANKS PA, BOLLEN TL, DERVENIS C, GOOSZEN HG, JOHNSON CD, SARR MG *et al.* Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*, 2013, **62** : 102-111.
18. KHATUA B, EL-KURDI B, SINGH VP. Obesity and pancreatitis. *Curr Opin Gastroenterol*., 2017, **33** : 374-382.
19. GONZALEZ-PEREZ A, SCHLIENGER RG, RODRIGUEZ LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study. *Diabetes Care*, 2010, **33** : 2580-2585.
20. LAI SW, MUO CH, LIAO KF, SUNG FC, CHEN PC. Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan. *Am J Gastroenterol*., 2011, **106** : 1697-1704.
21. HUH JH, JEON H, PARK SM, CHOI E, LEE GS, KIM JW *et al.* Diabetes Mellitus is Associated With Mortality in Acute Pancreatitis. *J Clin Gastroenterol*., 2018, **52** : 178-183.
22. YANG TL, SHEN MC, YU ML, HUANG YB, CHEN CY. Acute pancreatitis in patients with type 2 diabetes mellitus treated with dipeptidyl peptidase-4 inhibitors. *J Food Drug Anal*., 2016, **24** : 450-454.
23. TREACY J, WILLIAMS A, BAIS R, WILLSON K, WORTHLEY C, REECE J *et al.* Evaluation of amylase and lipase in the diagnosis of acute pancreatitis. *ANZ J Surg*., 2001, **71** : 577-582.
24. LIU F, LONG X, ZHANG B, ZHANG W, CHEN X, ZHANG Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. *Clin Gastroenterol Hepatol*., 2020, **18** : 2128-2130 e2122.
25. CHEUNG KS, HUNG IFN, CHAN PPY, LUNG KC, TSO E, LIU R *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. *Gastroenterology*, 2020, **159** : 81-95.
26. SCHEPIS T, LARGHI A, PAPA A, MIELE L, PANZUTO F, DE BIASE L *et al.* SARS-CoV2 RNA detection in a pancreatic pseudocyst sample. *Pancreatology*., 2020, **20** : 1011-1012.
27. PIEPER-BIGELOW C, STROCCHI A, LEVITT MD. Where does serum amylase come from and where does it go? *Gastroenterol Clin North Am*., 1990, **19** : 793-810.