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CLINICAL STUDY

Evaluation of patients with acute pancreatitis associated with SARS-CoV-2 (COVID-19); The importance of lipase/ /lymphocyte ratio in predicting mortality

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ABSTRACT

BACKGROUND: SARS-CoV-2 is the cause of a pandemic with high mortality. In the present study, the effects of the lipase/lymphocyte ratio on mortality were investigated in cases diagnosed with Covid-19 and acute pancreatitis.

METHODS: A total of 21 patients who were diagnosed with Covid-19 and acute pancreatitis, 34 patients who were not diagnosed with COVID-19 but diagnosed with acute pancreatitis, and 55 healthy control groups were divided into 3 groups and included in the study retrospectively. The patients who had positive RT-PCR (real-time polymerized chain reaction) test results were included in the study. Complete blood count and biochemical values of the patients were compared with those of the control group.

RESULTS: When the data of the cases diagnosed with COVID-19 and acute pancreatitis were examined retrospectively, the amylase, lipase, lipase/lymphocyte ratio, and D-dimer levels were found to be significantly higher than in the control group ($p < 0.01$). In the ROC analysis, the amylase, lipase, and lipase/lymphocyte ratio had a high AUC (area under the curve) value (0.993 / 0.949 / 0.978, respectively).

CONCLUSION: The lipase/lymphocyte ratio can be used in cases diagnosed with Covid-19 and acute pancreatitis to predict mortality *(Tab. 3, Fig. 3, Ref. 23)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, acute pancreatitis, lipase/lymphocyte ratio.

Introduction

The SARS-CoV-2 disease pandemic started in China/Wuhan at the end of 2019 (COVID-19). Many people have died since then (1). With its high contagiousness, people have had to be hospitalized and live in long-term quarantine. Its various mutations still maintain the disease-causing effects. Also, it was shown in many studies that COVID-19 and its variants cause high morbidity and mortality (2–4).

SARS-CoV-2 is a beta coronavirus and enters the cell by binding to the angiotensin-converting enzyme II (ACE II) receptor (5). The first virus samples that were isolated in China showed two subtypes: type L (70 %) and type S (30 %) (7). There are ACE2 receptors in the pancreatic Langerhans islet beta-cells, and it was reported that these receptors play roles in the development of hyperglycemia and diabetes mellitus (8, 9). Pancreatic damage caused by SARS-CoV-2 was reported in several case series, but there are not adequate data on the effects of this condition on the course of the disease and the differences it may cause during the treatment and follow-up (5, 6).

By analyzing clinical classification scores and biochemical parameters, the study aims to investigate the effects of the development of acute pancreatitis, in which the virus, which is the causative agent of COVID-19, plays roles in etiology, mortality, and clinical course.

Materials and methods

Study design and participants

The present paper was designed as a retrospective study and approved by the Ethics Committee of Ankara City Hospital/Turkey (2021–2047). The cases diagnosed with simultaneous COVID-19 and acute pancreatitis in Ankara City Hospital between April 1, 2020, and September 1, 2021, were included in the study.

The demographic, clinical, and laboratory data, and radiological findings of the patients were obtained from the electronic medical records and hospital computer case record forms. The cases were divided into 3 groups, namely non-COVID-19 pancreatitis group, COVID-19 with pancreatitis group and healthy control group. The values of the patients at the time of admission

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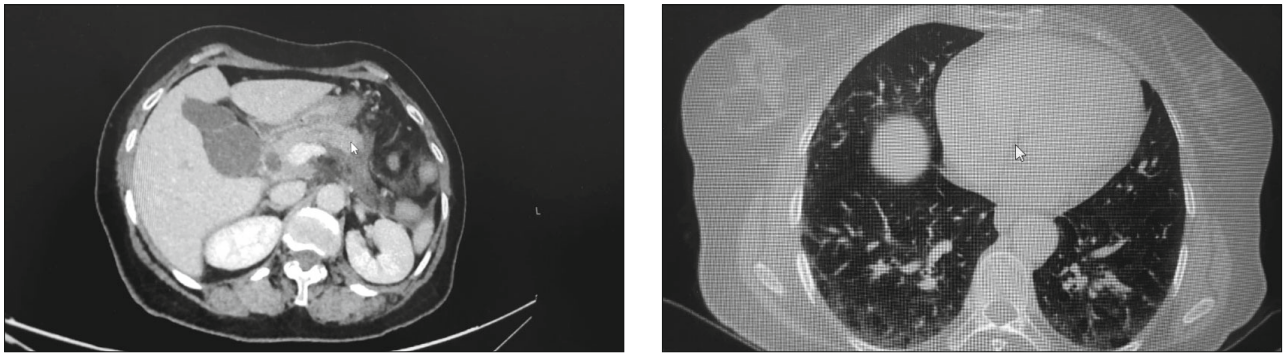

Fig. 1. The tomography images of a case diagnosed with COVID-19 and acute pancreatitis.

were recorded by using the computer follow-up program, and the groups were compared. The values of albumin, total protein, glucose, urea, creatinine, ferritin, ALT, AST, ALP, GGT, LDH, total bilirubin, conjugated bilirubin, amylase, lipase, creatinine kinase (CK), CRP, procalcitonin, D-dimer, full blood count, N/L ratios, and lipase/lymphocyte ratio were analyzed in all groups.

The clinical, laboratory and radiological findings of the patients were evaluated along with their demographic data to assess the acute pancreatitis criteria. Pancreatitis rate, length of hospital stay, and mortality rates were analyzed in each category. The chest and abdominal CT imaging findings were also evaluated as for the detection of COVID-19 pneumonia and pancreatic damage, while Balthazar scores were noted. The Balthazar score is a subscore of CT severity (10).

Diagnostic criteria

The oropharyngeal/nasopharyngeal swab samples for RT-PCR, routine blood tests, and those with the typical appearance in chest

Tab. 1. The demographic characteristics of the groups.

Variables	Total (n=55)	COVID-19 negative acute pankreatitis group (Grup N) (n=34)	COVID-19 positive acute pankreatitis group (Grup P) (n=21)	p
Baseline characteristics				
Age, years	60.3 ± 17.9	58.2 ± 18.5	63.7 ± 16.8	0.393
Gender, male/female	31/24	17/17	14/7	0.226
Outcome characteristics				
Mortality, (%)	7 (12.7)	1 (2.9%)	6 (28.6)	**0.006**
Comorbidities, (%)	40 (72.7)	22 (64.7)	18 (85.7)	0.089
Systemic hypertension, (%)	19 (34.5)	11 (32.4)	8 (38.1)	0.663
Diabetes mellitus, (%)	15 (27.3)	10 (29.4)	5 (23.8)	0.650
Cardiovascular organ failure, (%)	4 (7.3)	1 (2.9)	3 (14.3)	0.115
Renal organ failure, (%)	4 (7.3)	3 (8.8)	1 (1.6)	0.573
Cancer, (%)	5 (9.1)	2 (5.9)	3 (14.3)	0.292
Respiratory organ failure, (%)	7 (12.7)	5 (14.7)	2 (9.5)	0.575
Symptoms at admission, (%)				
Fever	1 (1.8)	0 (0)	1 (4.8)	–
Respiratory complaints	7 (12.7)	1 (2.9)	6 (28.6)	**0.006**
Abdominal pain	39 (70.9)	28 (82.4)	11 (52.4)	**0.017**
Vomiting/nausea	17 (30.9)	11 (32.4)	6 (28.6)	0.768
Pancreatitis-related characteristics				
Pancreatitis according to the Ranson criteria, n (%)				
Mild	44	33	11	**<0.001**
Moderate	0	0	0	–
Severe	11	1	10	**<0.001**
Pancreatitis according to the revised Atlanta criteria, n (%)				
Mild	44	30	14	0.052
Moderate	4	4	0	–
Severe	7	0	7	–
Pancreatitis according to the Balthazar criteria, n (%)				
Mild	50	32	18	0.292
Moderate	5	2	3	0.292
Severe	0	0	0	–

Tab. 2. The laboratory findings of the groups.

Characteristics	Control group (Grup 1) (n=63)	COVID-19 negative acute pancreatitis group (Grup 2) (n=34)	COVID-19 positive acute pancreatitis group (Grup 3) (n=21)	p*	p**
Age, Mean±SD, range, years	50.9±14.3, 22–79	58.2±18.5, 21–93	63.7±16.8, 28–86	**0.005**	C vs GN, p=0.121 C vs GP, **p=0.006** GN vs GP, **p=0.634**
Gender, male/female	34/29	17/17	14/7	0.466	–
Albumin, g/L	46.5±4.4	42.2±3.9	36.9±5.5	**<0.001**	C vs GN, **p< 0.001** C vs GP, **p< 0.001** GN vs GP, **p<0.001**
Total protein, g/L	70.7±4.2	65.6±6.1	61.9±7.5	**<0.001**	C vs GN, **p< 0.001** C vs GP, **p< 0.001** GN vs GP, p=0.054
WBC, $x10^9$/L	9.2±4.2	9.6±3.2	9.4±4.2	0.853	–
NEU, $x10^9$/L	6.0±4.4	7.4±3.3	7.8±4.3	0.124	–
Lymphocytes, $x10^9$/L	2.2±1.0	1.5±0.7	1.7±3.5	0.104	–
Hemoglobin, g/dL	13.6±1.6	13.7±1.7	12.3±2.6	**0.006**	C vs GN, p=1.000 C vs GP, **p=0.012** GN vs GP, **p=0.010**
Platelet, $x10^9$/L	259.9±75.0	229.6±81.0	284.2±122.7	0.069	–
Hematocrit, %	40.0±4.5	41.9±4.9	37.8±6.8	**0.016**	C vs GN, p=0.266 C vs GP, p=0.252 GN vs GP, **p=0.013**
N/L	3.4±2.9	7.2±6.5	13.8±19.3	**<0.001**	C vs GN, p=0.177 C vs GP, p=0.067 GN vs GP, **p=0.031**
CRP, g/L	0.04±0.02	0.04±0.05	0.05±0.04	0.862	–
PCT, µg/L	0.06±0.09	1.06±3.46	3.6±10.9	**0.023**	C vs GN, p=1.000 C vs GP, p=**0.018** GN vs GP, p=0.221
D-dimer, mg/L	0.4±0.3	1.6±1.7	2.9±2.0	**<0.001**	C vs GN, **p=0.001** C vs GP, **p <0.001** GN vs GP, **p=0.001**
Troponin I H ng/L	2.4±1.9	6.5±12.4	53.9±95.6	**<0.001**	C vs GN, p=1.000 C vs GP, **p <0.001** GN vs GP, **p <0.001**
Amylase, U/L	64.8±21.8	1236.6±1290.3	958.1±1275.3	**<0.001**	C vs GN, **p < 0.001** C vs GP, **p <0.001** GN vs GP, p=0.764
Lipase, U/L	31.9±8.6	1858.9±1839.6	1519.4±1966.8	**<0.001**	C vs GN, **p < 0.001** C vs GP, **p <0.001** GN vs GP, p=1.000
Lipase/ lymphocytes	21.6±33.6	1519.2±1439.9	2203.8±2673.9	**<0.001**	C vs GN, **p < 0.001** C vs GP, **p <0.001** GN vs GP, p=0.234
AST, U/L	21.7±12.8	252.6±281.5	239.8 ±447.0	**<0.001**	C vs GN, **p< 0.001** C vs GP, **p=0.002** GN vs GP, p=1.000
ALT, U/L	30.9±22.0	247.7±245.4	174.2±241.3	**<0.001**	C vs GN, **p < 0.001** C vs GP, **p=0.003** GN vs GP, p=0.347
GGT, U/L	27.4±18.0	336.2±342.1	283.4±356.8	**<0.001**	C vs GN, **p< 0.001** C vs GP, **p <0.001** GN vs GP, p=1.000
LDH, U/L	208.7±44.4	435.9±424.5	489.2±301.7	**<0.001**	C vs GN, **p< 0.001** C vs GP, **p <0.001** GN vs GP, p=1.000
Na, mEq/L	139.6±3.0	137.7±3.8	139.9±5.9	0.073	–
K, mEq/L	4.2±0.4	4.0±0.6	4.3±0.7	0.222	–

Tab. 2.

Characteristics	Control group (Grup 1) (n=63)	COVID-19 negative acute pancreatitis group (Grup 2) (n=34)	COVID-19 positive acute pancreatitis group (Grup 3) (n=21)	p*	p**
Ca, mg/dL	9.3±0.5	9.0±0.5	8.5±2.2	**0.016**	C vs GN, p=1.000 C vs GP, **p=0.012** GN vs GP, p=0.182
Glucose, mg/dL	102.7±26.6	166.3±107.3	171.8±103.9	**<0.001**	C vs GN, **p=0.001** C vs GP, **p=0.001** GN vs GP, p=1.000
Urea, mg/dL	30.7±9.8	40.9±23.7	74.3±61.9	**<0.001**	C vs GN, **p < 0.001** C vs GP, p=0.358 GN vs GP, **p <0.001**
Creatinine, mg/dL	0.5±0.4	1.1±1.2	1.2±0.8	**<0.001**	C vs GN, **p=0.001** C vs GP, **p<0.001** GN vs GP, p=1.000
Lactate, mmol/L	1.5±0.7	2.0±0.9	1.8±0.7	**0.047**	C vs GN, **p=0.047** C vs GP, p=0.812 GN vs GP, p=1.000
PT, sec	14.4±13.1	12.3±1.4	14.4±6.7	0.600	–
aPTT, sec	24.2±3.5	23.6±4.3	24.9±4.3	0.522	–

computed tomography were taken for the diagnosis of COVID-19. Those with fever and respiratory symptoms according to the WHO interim guidelines regarding the diagnosis of COVID-19, pneumonia findings on CT, or clinical signs based on positive SARS-CoV-2 PCR results were included in the study.

Pancreatitis diagnosis was made according to the patient's symptoms, laboratory findings, and abdominal imaging findings. Typical abdominal pain, serum amylase and upper limit of lipase were found to be elevated 3-fold or more, and imaging (abdominal CT or MRI with IV contrast) findings were also evaluated. The diagnosis was made by the presence of at least two of three findings as follows: Ranson criteria, Balthazar CTSI (computed tomography severity index), and severe clinical manifestation as evaluated with the revised Atlanta criteria (11). The COVID-19 patients whose amylase and lipase values increased 3-fold or more in addition to clinical and radiological findings were placed in Group 3 (n=21), and patients who were diagnosed with acute pancreatitis with these criteria but did not have any risk of being infected with COVID-19 formed the Group 2 (n=34). A total of 55 healthy individuals (n=55), who were completely healthy were assigned as the control group – Group 1. The tomography images of a case diagnosed with COVID-19 and acute pancreatitis are shown in Figure 1.

Statistical analysis

The Statistical Package for Social Sciences for Windows, version 22 (IBM, Armonk, NY, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was used for normality of variables. Descriptive analysis was indicated using mean±standard deviation (SD) for the parameters with normal distribution, and median (interquartile range) (IQR) was used for non-normally distributed variables. One-way ANOVA test was used for parameters that were normally distributed. Non-normally distributed variables were evaluated with Kruskal–Wallis test. Comparisons for categorical variables were performed using the chi-square test or the Fisher's exact test. Receiver operation characteristic (ROC) curve was performed to analyze the efficiency of the COVID-19 group. The optimal cut-off values of the amylase, lipase, lipase/lymphocyte ratio, D-dimer, and NLR were calculated by applying the ROC analysis. The value of $p<0.05$ was considered to be statistically significant.

Results

A total of 21 inpatients who were diagnosed with COVID-19 according to the WHO criteria were included in the study (1). The demographic data of the cases who were included in the study, their comorbidities, complaints at admission to the Emergency Department, and the data on Ranson, Atlanta and Balthazar criteria are given in Table 1.

The most common symptoms in the pancreatitis groups at admission to the hospital was abdominal pain ($p=0.017$). Comorbidities were detected in 18 patients (85.7 %), and they were higher in the COVID-19 (-) group ($p=0.089$). The most common comorbidities were systemic hypertension, diabetes mellitus, and cardiovascular diseases, respectively.

The hemogram and biochemical parameters and statistical analysis of all groups are given in Table 2. The values of amylase, lipase, D-dimer, AST, ALT, GGT, LDH, glucose, urea, creatinine, and lipase/lymphocytes ratio were significantly higher in both groups when compared to the control group while the total protein and albumin levels were significantly lower ($p<0.001$) (Fig. 2).

The ROC analysis of routine blood parameters to predict prognosis in patients diagnosed with COVID-19 and acute pancreatitis

The ROC curve analysis was used to determine the effectiveness of various parameters to predict the prognosis in the group that was diagnosed with COVID-19 and acute pancreatitis (Fig. 3).

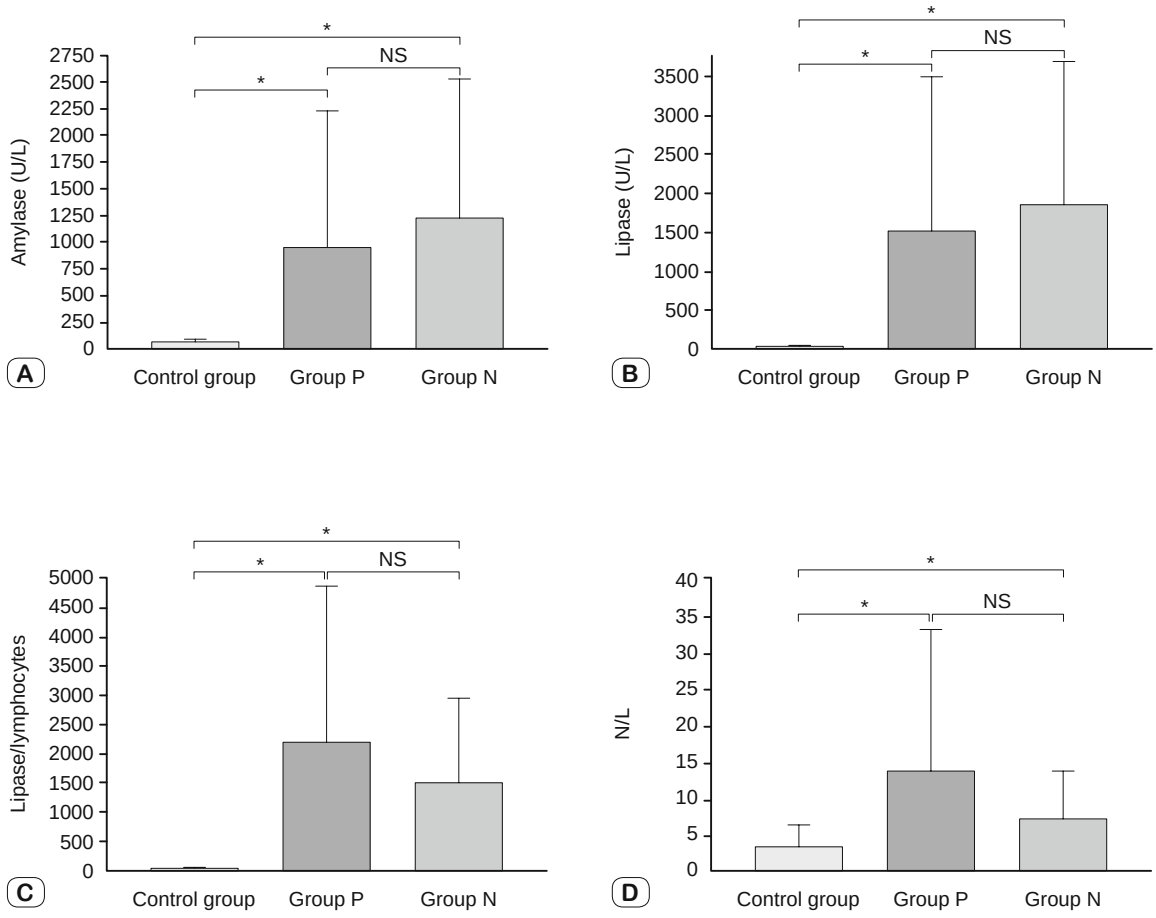

Fig. 2. Comparison of amylase (A), lipase (B), lipase/lymphoctes ratio (C), and N/L (D) levels.

In ROC analysis, the values of amylase, lipase/lymphocytes ratio and lipase had high AUC (area under the curve) values, namely 0.993, 0.978, and 0.949, respectively; $p<0.001$. These results show that all three parameters are diagnostic. The AUC, optimal cut-off value, and sensitivity and specificity values of the laboratory parameters are given in Table 3.

Discussion

The COVID-19 pandemic continues to affect the entire world in various aspects. Pancreatic involvement can also be seen, especially in SARS-COV2 cases that involve the lungs and multiple organs. Our study, in which the data of COVID-19 patients who were PCR-positive and also diagnosed with acute pancreatitis were evaluated, was conducted in a single center. There is a study showing that the rate of development of acute pancreatitis increases in COVID-19 cases, which affects the prognosis (12). We also think that our study will make a significant contribution in terms of providing a new alternative in the prognosis in cases diagnosed with COVID-19 and acute pancreatitis.

The urea and creatinine levels were significantly higher in COVID-19 cases with acute pancreatitis in our study ($p<0.001$). These were considered to be associated with poor prognosis and increased mortality levels (13, 14).

Tab. 3. Routine blood parameters in the diagnosis of patients with COVID-19 and acute pancreatitis group taken at admission

Variables	Cut-off value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	p
AST	≥ 23.5	0.838 (0.720–0.956)	84.2	75.0	**<0.001**
ALT	≥ 23.5	0.666 (0.499–0.833)	63.2	51.7	**0.030**
N/L	≥ 4.0	0.820 (0.720–0.920)	84.2	70.0	**<0.001**
Amylase	≥ 111.0	0.993 (0.981–1.000)	94.7	96.7	**<0.001**
Lipase	≥ 50.5	0.949 (0.851–1.000)	94.7	98.3	<0.001
Lipase/lymphocytes	≥ 52.9	0.978 (0.940–1.000)	94.7	96.7	**<0.001**
CRP	≥ 0.03	0.464 (0.290–0.638)	52.6	35.0	0.638
D-dimer	≥ 1.1	0.965 (0.925–1.000)	89.5	96.7	**<0.001**
WBC	≥ 7.9	0.546 (0.394–0.697)	63.2	55.0	0.551

AUC – area under the curve; N/L – neutrophils-to-lymphocytes ratio. Asymptotic significance – less than 0.05 was considered significant

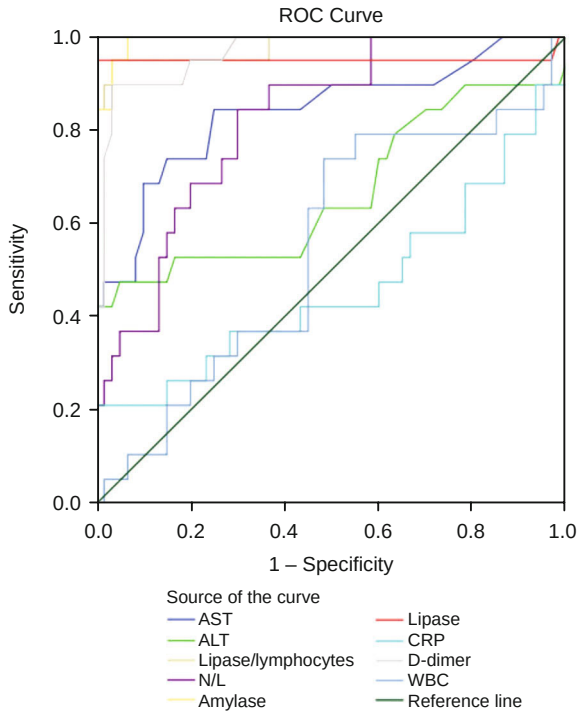

Fig. 3. The ROC analysis of routine blood parameters to predict prognosis in patients diagnosed with COVID-19 and acute pancreatitis.

Increased D-dimer levels and lymphopenia were associated with higher mortality in COVID-19 patients (15). In our study, D-dimer levels were the highest in the COVID-19^{+} with pancreatitis group. There was no significant difference in neutrophil and lymphocyte levels, and NLR levels were significantly higher. Even if the white blood cell count was in the normal range, NLR was shown to play roles in predicting the prognosis of chronic and acute inflammatory processes (16). In conclusion, the coexistence of COVID-19^{+} and pancreatitis is a finding suggesting high mortality.

Many studies evaluated the epidemiological and clinical findings of COVID-19, however, the data on pancreatic tissue damage caused by COVID-19 are rare (17). Some publications reported pancreatitis cases caused by SARS-CoV-2 (18, 19, 20).

In previous studies, it was reported that ACE-II (angiotensin II) is expressed in the pancreas, especially from islet cells. It was also reported that the damage to ACE-II results in hyperglycemia and development of DM through these receptors. It is already known that SARS-CoV-2 acts by binding to ACE-II. Liu et al. showed that there was ACE-II expression in pancreatic tissue in eight donors and reported that SARS-CoV-2 might cause pancreatic tissue damage (21). This action mechanism suggests that pancreatic tissue is a potential target of SARS-CoV-2, which may develop through ACE-II receptors causing both acute pancreatitis and DM development (21, 22). For these reasons, it is possible that in our study, the etiology in 21 cases who were diagnosed with COVID-19 and also developed pancreatitis is associated with COVID-19

The amylase and lipase values, which are biochemical markers in showing pancreatic damage, and abdominal tomography were included in the diagnosis. In our study, there were increased levels of serum amylase and lipase, which are biochemical markers of pancreatic damage. In our study which included 21 cases of pancreatitis and COVID-19, all patients had pancreatic damage findings in their tomography. In a previous study, it was emphasized that pancreatic damage with elevated amylase and lipase levels developed in 52 moderate COVID-19 cases (23). However, the lack of clinical and radiological findings in this study could not provide adequate evidence to show pancreatic damage. In our study, the Ranson, Balthazar and revised Atlanta scores of the cases were also determined. The Ranson criteria were insufficient in evaluating the severity of COVID-19 pneumonia with biochemical values only, and the Balthazar score was insufficient in estimating mortality because it only evaluated the pancreas with abdominal tomography findings. The revised Atlanta score was more significant in evaluating the coexistence of COVID-19 and pancreatitis. In the revised Atlanta score, mortality was more significant in estimation because abdominal tomography, biochemical values, and clinical organ damage were evaluated. As a matter of fact, 7 cases were in the severe class according to the Atlanta score, which shows that acute pancreatitis is a risk factor for COVID-19-related mortality independent of comorbidities.

There are publications that report the optimum cut-off value of some serum biochemical parameters as prognostic indicators in COVID-19 by using the severe disease ROC curve (11, 12). It was found in our study that amylase, lipase, lipase/lymphocyte ratio, and D-dimer parameters had the highest AUC values (0.993, 0.949, 0.978, 0.965, respectively) in predicting the severity of the disease in patients with positive COVID-19 and acute pancreatitis in ROC curve analysis. Since the lipase/lymphocyte ratio plays important roles in the pathogenesis of both diseases, it can be useful in estimating mortality and prognosis.

Conclusion

Lipase/lymphocyte ratio can be used in cases diagnosed with COVID-19 and acute pancreatitis to predict mortality.

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