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Evaluating the effect of SARS-Cov-2 infection on prognosis and mortality in patients with acute pancreatitis

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ABSTRACT

Introduction: Acute pancreatitis (AP) is the leading cause of hospitalization among gastrointestinal disorders. The aim of our study is to compare the results between AP patients with and without COVID−19, and to reveal the effects of COVID−19 on the course, intensive care needs and mortality of AP patients.
Material methods: This was a single-center, retrospective and observational study. Patients over 18 years of age, who were diagnosed with AP during the current pandemic. According to the RT-PCR test result, patients were divided into two groups: COVID-19 positive and COVID-19 negative. Gender, age, laboratory parameters, intensive care unit admission, length of hospital stay, severity and mortality of AP were compared between these two groups.
Results: We reviewed 562 patients presenting to the emergency department who were diagnosed with acute pancreatitis between 10.03.2020 and 31.12.2020 and included 189 patients in our study. Positive patients need for intensive care (7.23%) were higher compared to negative patients (0.94%). 32.53% of positive patients and 14.15% of negative patients had severe AP ($p < 0.03$). We established that being COVID-19 positive, CCI scores of ≥5, presence of COVID-19 compatible pneumonia on CT and BISAP scores had an effect on mortality ($p < 0,05$).
Conclusion: The severity and mortality of AP increase in patients with both AP and COVID-19. This rate increases even more in the presence of COVID-19-associated pneumonia. We believe that new strategies should be developed for the follow-up and treatment of patients with both these conditions.

1. Introduction

Acute pancreatitis (AP) is the leading cause of hospitalization among gastrointestinal disorders in the United States of America (USA) [1,2]. It is most commonly caused by gallstones and alcohol use; however, there have been rare reports of AP with a viral etiology [3,4]. There are reports on acute pancreatitis cases with concomitant severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection that has affected the entire world [5-8]. The first SARS-CoV-2 case in Turkey was identified on March 10, 2020. The number of cases did not increase upon the measures taken, and normalization was started gradually on June 1, 2020. However, an earthquake occurred in our city on October 30, 2020, and both the search and rescue efforts and the fact that many people became homeless, resulting in an increase in contact between people and in our patient density. Especially on November 15–25, 2020, a sudden increase occurred in the number of cases both in Izmir and across Turkey. This period, in which all hospitals were designated as COVID-19 referral hospitals and most of the emergency services served as intensive care units, was still ongoing as of January 1, 2021, the end of the time period of this study [9].

The Angiotensin Converting Enzyme-2 (ACE2) receptors used by SARS-CoV-2 to enter the cell were detected in pancreatic islet cells besides the respiratory tract [10-12]. It was suggested that by binding to these receptors, SARS-CoV-2 might enter pancreatic cells and cause acute pancreatitis itself or cause pancreatic injury through the cytokine storm during the infection, and the coexistence of AP and SARS-CoV-2 infection might affect the course of AP [13-16].

In this study, we examined patients presenting to the emergency department during the pandemic who were diagnosed with acute pancreatitis after medical examinations and hospitalized due to AP. The aim of our study is to compare the results between AP patients with and without coronavirus disease of 2019 (COVID-19) and to evaluate the effects of COVID-19 on the outcome, need for intensive care unit admission, and mortality of AP patients.

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2. Materials and methods

2.1. Study design and setting

This was a single-center, retrospective, and observational study. The study was initiated upon the approval by the Turkish Ministry of Health dated 02.01.2021 and numbered T15–58-55, and the approval by İzmir Katip Çelebi University Ethics Committee dated 21.01.2021 and numbered 002. Our study was conducted with patients meeting the inclusion criteria who presented to the emergency department of our hospital between 11.03.2020, the date of the first official COVID-19 case in Turkey, and 31.12.2020.

2.2. Study population

The hospital automation system was used to screen patient records according to the ICD-10 (K85) diagnosis code. Patients over 18 years of age, who did not have any trauma, who were not pregnant, who had no hematological malignancy, who were diagnosed with Acute Pancreatitis according to the Revised Atlanta Criteria, and who had sufficient data in their records were included in the study [17].

2.3. Data collection

Patient data on age, gender, and comorbidities were recorded. Comorbidities were classified according to the Charlson Comorbidity Index (CCI) [18]. The White Blood Cell (WBC) count, Lymphocyte (LYM) count, Neutrophil (NEU) count, Neutrophil-to-Lymphocyte Ratio (NLR), Hematocrit (HCT), Red Cell Distribution Width (RDW), Platelet (PLT) count, and C-Reactive Protein (CRP), D-Dimer, Ferritin, and Procalcitonin (PCT) levels from the blood tests on admission to the emergency department, and imaging results were recorded. The etiological factors of AP that could be identified by etiological factors were recorded by examining the results from anamnesis (alcoholism), family history (genetic diseases), laboratory findings (hyperlipidemia), and routine examinations such as ultrasonography and from examinations performed until the patient's discharge/death, such as computerized tomography, endoscopic ultrasonography, magnetic resonance cholangio pancreatography (MRCP) and endoscopic retrograde cholangio pancreatography (ERCP). Patients with no etiological factor identified after examinations were recorded as “with no etiological factor.”

The severity of AP was determined according to the Bedside Index of Severity in Acute Pancreatitis (BISAP) score [19]. Patients with a BISAP score of ≥3 were classified as having severe AP, and patients with a BISAP score of ≤2 as having mild AP [20].

For COVID-19 pneumonia, the Thoracic Computed Tomography (TCT) findings were assessed according to the Radiological Society of North America (RSNA) criteria [21]. Patients reported as type 1 and type 2 were considered COVID-19 compatible (Group 1), while patients reported as type 3 and type 4 were considered COVID-19 incompatible (Group 2).

Treatment methods were evaluated. Patients who underwent interventional procedures (ERCP, PTC), surgical interventions (cholecystectomy, etc.) and medical therapy for AP treatment were recorded. The number of days' patients stayed in the hospital (intensive care/service), AP-related complications and mortality were recorded.

The COVID-19 diagnosis was established by nasopharyngeal swab specimen Real-Time Reverse Transcription Polymerase Chain Reaction testing (Biospeedy® RT-PCR test) as recommended by Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Fifth Version for Trial) [22]. Patients who tested negative for two tests were considered negative. According to the RT-PCR test result, patients were divided into COVID-19-positive and COVID-19-negative groups. The data were compared between these two groups.

2.4. Statistical method

The study data were assessed using IBM SPSS Statistics Version 20. The use of parametric or nonparametric tests was decided by analyzing the normality of the quantitative data using the One-Sample Kolmogorov-Smirnov test. Frequency and percentage distribution were calculated for descriptive statistics and mean, standard deviation, median, minimum and maximum values for continuous variables. The Pearson's Chi-Square and Fisher's Exact-tests were used to compare categorical variables between groups. Differences between laboratory values and COVID-19 test results were analyzed by the Mann-Whitney *U* test. Also, laboratory parameters were assessed by comparing COVID-19 positive and negative acute pancreatitis patients, and a ROC analysis was conducted for variables found to differ between positive and negative patients. The cut-off values were calculated for variables with a statistical difference. A logistic regression model was used to analyze factors affecting mortality. Statistical significance level was set at $p < 0.05$.

3. Results

We retrospectively reviewed 562 patients presenting to the emergency department who were diagnosed with acute pancreatitis between 10.03.2020 and 31.12.2020. Among these patients, 189 patients who met the inclusion criteria and had sufficient data in their records were included. The rate of COVID-19 positive patients was 43.92%. Of the patients, 47.6% were male and had a mean age of 54.56 ± 16.90 years ($n = 90$), while the mean age of female patients was 55.24 ± 19.00 years ($n = 99$).

The patients were divided into COVID-19-positive and COVID-19-negative groups. No statistically significant difference was observed between the groups in terms of gender and age. Considering the distribution of comorbidities, the rate of patients with CCI ≥ 5 was significantly higher in positive patients compared to negative patients. The assessment of etiological factors for AP did not reveal any etiological factor in 40.96% and 24.53% of positive and negative patients, respectively ($p < 0.05$). The assessment of thoracic CT scans for COVID-19 pneumonia findings, in turn, revealed the typical appearance of COVID-19 pneumonia in 33.73% and suspicious COVID-19 pneumonia findings in 40.96% of positive patients ($p < 0.05$). There was no COVID-19 compatible finding on thoracic CT in 89.52% of negative patients. The comparison of the severity of AP according to the BISAP score showed that 32.53% of positive patients and 14.15% of negative patients had severe AP, with a statistically significant difference between the two groups ($p < 0.03$). When the outcomes of the patients were examined, we found a higher number of positive patients with the need for intensive care (7.23%) compared to negative patients (0.94%). There was enormously significant difference (7.69-fold) ($p < 0.02$). The mean length of hospital stay was 6.4 days for overall patients, 7.7 days for positive patients, and 5.5 days for negative patients ($p < 0.02$). Considering mortality, we found that 15.66% of positive patients died when compared to 2.83% of negative patients, revealing a statistically significant difference between the groups ($p < 0.02$) (Table 1).

To determine the factors affecting mortality, we compared the variables between non-surviving and surviving patients using the Chi-square test. The test revealed etiology, stay in the intensive care unit/ward, hospitalization length, treatment, CCI score, COVID-19 positivity, CT findings and BISAP score to be statistically significant (Table 2), and when we used a multivariate logistic regression model to analyze the effects of these variables on mortality, the dependent variable, we found an Adjusted R-Squared value of 0.373. This value suggests that non-survival (mortality) is not explained by these variables in a significant way. In addition, 6 of the 8 independent variables were categorical and this would cause the model to be erroneous or misinterpreted. The effects of the non-categorical variables, BISAP score and CT findings, on mortality were analyzed using a binary logistic regression model.

Table 1
Demographic characteristics of patients, COVID-19 positive-negative status and distribution of variables

Variables	Category	Total (n)	%	Negative (n)	%	Positive (n)	%	*p*
Gender	Male	90	47,6	48	45,28	42	50,60	0,194
	Female	99	52,4	58	54,72	41	49,40	
Age	Male mean ± SD	54,56 ± 16,90 (n = 90)	47,62	52,21 ± 17,21 (*n* = 48)	45,28	57,24 ± 16,34 (*n* = 42)	50,60	0,476
	Female mean ± SD	55,24 ± 19,00 (n = 99)	52,38	53,55 ± 17,16 (*n* = 58)	54,72	57,63 ± 21,23 (*n* = 41)	49,40	
	Total mean ± SD	54,92 ± 17,99 (n = 189)	100,0	52,94 ± 17,12 (*n* = 106)	100,00	57,43 ± 18,85 (*n* = 83)	100,00	
CCI score	0	67	35,64	43	40,95	24	28,92	0,029
	1_3	57	30,32	33	31,43	24	28,92	
	3_5	33	17,55	19	18,10	14	16,87	
	5>	32	16,49	10	9,52	22	25,30	
Etiology	Divisium	1	0,53	1	0,94	0	0,00	0,016
	Tumor	9	4,76	6	5,66	3	3,61	
	Hyperlipidemia	11	5,82	10	9,43	1	1,20	
	Stent obstruction	1	0,53	0	0,00	1	1,20	
	Bile sludge	4	2,12	2	1,89	2	2,41	
	Bile stone	103	54,50	61	57,55	42	50,60	
	Exist	129	68,25	80	75,47	49	59,04	
	None	60	31,75	26	24,53	34	40,96	
CT findings	1.Group	70	36,7	7	6,66	63	74,69	0,00
	2.Group	119	63,3	98	93,34	21	25,31	
BISAP Score	0–1-2	147	77,8	91	85,85	56	67,47	0,03
	≥3	42	22,2	15	14,15	27	32,53	
Hospitalization	ICU	7	3,7	1	0,94	6	7,23	0,02
	Ward	182	96,3	105	99,06	77	92,77	
Complication	Abscess	12	6,3	7	6,60	5	6,02	0,92
	Cyst	9	4,8	7	6,60	2	2,41	
	Necrosis	26	13,8	12	11,32	14	16,87	
	None	142	75,1	80	75,47	62	74,70	
Treatment	Surgical	25	13,2	14	13,21	11	13,25	0,01
	ERCP	68	36,0	51	48,11	17	20,48	
	Medical	91	48,1	39	36,79	52	62,65	
	PTK	5	2,6	2	1,89	3	3,61	
Mortality	Ex	16	8,5	3	2,83	13	15,66	0,02
	Alive	173	91,5	103	97,17	70	84,34	

CCI score: Charlson Comorbidity Index, CT: computed tomography, Group 1: Radiological Society of North America Type 1–2, Group 2: Radiological Society of North America Type 3–4, BISAP score: Bedside index for severity in acute pancreatitis, ICU: Intensive care unit, ERCP: Endoscopic retrograde cholangiopancreatography, PTK: Percutaneous transhepatic cholangiography.

Both independent variables were found to have a significant effect on patient mortality. This is supported by the odds ratios of 0.013 and 0.011 seen in the table 3. Especially the Exp(B) value of BISAP Scores was calculated as 4.295 in the table, which suggests a strong effect on mortality (Table 3). When the values for the type of treatment and stay in the ICU/Ward, which are among the independent variables affecting the outcome of the patient, were examined, the Binary Logistic Regression model showed that stay in the intensive care unit or ward affected the status of survival/non-survival ($p = 0.00$). However, the effect on mortality could not be evaluated since the distribution of patients in the surgical, ERCP, Medical and PTC subgroups in the treatment variable as outliers caused a problem with equality of variances. (See Table 4.)

The examination of patients' laboratory parameters showed a statistically significant difference in WBC, NEU, LYM, NLR, CRP, D-dimer, Ferritin, and procalcitonin values between the groups ($p < 0.05$) (Table 5). According to the ROC curve analysis conducted to determine the power of the different parameters in discriminating between COVID-19 positive and negative patients, Ferritin and CRP had poor, WBC, NEU, and PCT had fair, and NLR and D-dimer had good diagnostic accuracy in determining COVID-19 positivity (Table 6).

When the laboratory parameters were evaluated according to the mortality status, mean CRP, ferritin, D-dimer, Procalcitonin, and NLR values were significantly different between the survivors and non-survivors. Further examination of these parameters using ROC curve analysis revealed a good correlation between mortality and CRP and ferritin values and a moderate and weak correlation between mortality and D-dimer, Procalcitonin NLR values (Table 7).

4. Discussion

The present study is the third in the literature to investigate the effects of SARS-CoV-2 infection among patients diagnosed with AP. Our study has the highest rate of COVID-19 positive patients. We established a greater risk for severe AP, need for intensive care, and risk of mortality in COVID-19 positive patients with AP than in COVID-19 negative patients with AP. There was an increased risk of mortality in patients with BISAP scores of ≥3 and CT findings of COVID-19compatible pneumonia. Unlike other studies, we found that inflammatory parameters also had an effect on mortality.

Among our study patients, 47.62% were male, and 46.7% of the male patients were COVID-19 positive. The mean age was 54.92 ± 17.99 years ($n = 189$), and our patient population was consistent with that of studies investigating the COVID-19 and AP relationship [13-15].

Among studies evaluating the relationship between COVID-19 and AP, Wang Fan et al. reported that 17% of 52 COVID-19 patients developed pancreatic injury (PI) [23]. Likewise, Bruno et al. found that six patients hospitalized due to COVID-19 and developed Acute Respiratory Distress Syndrome (ARDS) had elevated pancreatic enzymes later [24]. In both studies, patients were classified as PI because the findings did not meet the AP diagnostic criteria [23,24]. Our difference from these studies was that our study patients met the AP diagnostic criteria. Similarly, Szatmary et al. assessed five AP patients who were positive for COVID-19 and reported no etiological factor for AP [6]. Similar to our study, Inamdar et al. and Pandanaboyana et al. compared AP patients with and without COVID-19 and identified alcohol use as the most common cause of AP in negative patients, while no etiological factor was

Table 2
Comparison of variables between deceased and living patients

Variables	Category	Deceased (n)	%	Alive (n)	%	P
Gender	Male	8	50	82	47,4	0,842
	Female	8	50	91	52,6	
Age	Male mean ± SD	66,13 ± 15,43 (n = 8)	50	53,43 ± 16,70 (*n* = 82)	47,398,844	0,442
	Female mean ± SD	75,50 ± 12,35 (n = 8)	50	53,43 ± 18,48 (*n* = 91)	52,601,156	
CCI Score	0	1	6,3	67	38,7	0,00
	1–3	3	18,8	54	31,2	
	3–5	3	18,8	30	17,3	
	≥5	10	56,3	22	12,7	
Etiology	Divisium	0	0	1	0,6	0,00
	Tumor	5	31,3	3	1,7	
	hyperlipidemia	0	0	11	6,4	
	stent obs	1	6,3	0	0	
	Bile sludge	0	0	5	2,9	
	Bile stone	6	37,5	97	56,1	
	Exist	**12**	**75**	**117**	**67,6**	
	None	**4**	**25**	**56**	**32,4**	
CT findings	1.Group	14	81,3	56	32,4	0,002
	2.Group	3	18,8	116	67,1	
BISAP Score	≤2	6	37,5	141	81,5	0,00
	≥3	10	62,5	32	18,5	
Hospitalization	ICU	6	37,5	1	0,01	0,00
	Ward	10	62,5	172	99,9	
Treatment	Surgery	3	18,75	22	12,72	0,008
	Ercp	1	6,25	67	38,73	
	Medical	10	62,5	81	46,82	
	Ptk	2	12,5	3	1,73	
RT-PCR Test	Positive	13	81,25	70	40,46	0,002
	Negative	3	18,75	103	59,54	
Hospitalization length		**mean = 11,9 days**		**mean = 5,9 days**		0,000*

Not: (*) İndependent Sample t-Test *P* value.
CCI score: Charlson Comorbidity Index, CT: computed tomography, Group 1: Radiological Society of North America Type 1–2, Group 2:: Radiological Society of North America Type 3–4, BISAP score: Bedside index for severity in acute pancreatitis, RT-PCR: Real-Time Reverse Transcription Polymerase Chain Reaction.

Table 3
Logistic regression analysis of the effects of CT findings and BISAP score on mortality

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	BISAP(1)	1457	,585	6211	1	**,013**	4295	1365	13,514
	CT(1)	-1762	,691	6498	1	**,011**	,172	,044	,665
	Constant	2517	,705	12,731	1	,000	12,393		

[a] Variable(s) entered on step 1: bısapnew, ctnew.

identified in positive patients. Gallstones were found to be the most common etiology for both groups [14,15]. Our findings are consistent with these studies. Since the assessment of etiological factors could not identify any etiology for AP in the patients, Inamdar et al. and Pandanaboyana et al. suggested that AP could be caused directly by the cytopathic effect mediated by SARS-CoV-2 replication or the emerging inflammatory processes due to the presence of ACE2 receptors in the pancreas [14,15]. A postmortem study by Müller et al. with four patients who died due to COVID-19 visualized viral particles replicating in pancreatic endocrine cells [11]. In our study, the rate of patients without an etiology was higher in positive patients. The authors believe that in these patients, the increased expression of ACE2 receptors in the pancreas may increase the viral load, and SARS-CoV-2 may cause AP through the ACE2 receptors in pancreatic beta cells or AP may develop due to the inflammation activated by COVID-19. The reflection of increased inflammation in COVID-19 patients on the clinical condition of the patient is the Systemic Inflammatory Response Syndrome (SIRS) symptoms such as fever, tachycardia, and dyspnea [25]. In severe cases, septic shock and multiple organ dysfunction may occur. SIRS symptoms are also a parameter of the BISAP score that we use to assess

Table 4
Logistic regression analysis of the effects of treatment method and stay in the ICU/Ward on mortality

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**ICU/ward(1)**	**5002**	**1286**	**15,127**	**1**	**,000**	**148,719**	**11,958**	**1849,605**
	Treatment			9118	3	,028			
	Treatment (1)	-1957	1161	2841	1	,092	,141	,015	1375
	Treatment (2)	-4523	1550	8516	1	,004	,011	,001	,226
	Treatment (3)	-2287	1012	5111	1	,024	,102	,014	,738
	Constant	-,405	,913	,197	1	,657	,667		

ICU: intensive care unit.
[a] Variable(s) entered on step 1: ICU/ward, treatment method.

Table 5
Comparison of laboratory parameters of COVID-19 positive and negative patients

Laboratory parameters	All patients (N = 189)	Positive (n = 83)	Negative (n = 106)	P
	Mean ± Std.dev. (min-max)	Mean ± Std.dev. (min-max)	Mean ± Std.dev (min-max)	
WBC ($\times 10^3/\mu L$)	11,71 ± 4,58 (2,82-26,58)	13,78 ± 5,14 (2,82-26,58)	10,09 ± 3,29 (4,53-21,20)	0,000
NEU ($\times 10^3/\mu L$)	9,21 ± 4,60 (1,87-24,68)	11,69 ± 5,13 (1,87-24,68)	7,28 ± 2,96 (2,92-18,63)	0,000
LYM ($\times 10^3/\mu L$)	1,61 ± 0,94 (0,12-6,20)	1,23 ± 0,80 (0,12-4,73)	1,91 ± 0,94 (0,33-6,20)	0,000
NLR	9,98 ± 12,30 (0,42-85,00)	15,99 ± 15,69 (1,40-85,00)	5,28 ± 5,26 (0,42-42,60)	0,000
HCT (%)	37,82 ± 5,59 (17,40-51,10)	37,42 ± 6,00 (17,40-51,10)	38,13 ± 5,25 (22,90-50,40)	0,640
RDW (%)	14,21 ± 1,97 (11,10-22,90)	14,11 ± 1,95 (11,0-21,70)	14,29 ± 2,00 (11,60-22,90)	0,465
PLT ($\times 10^3/\mu L$)	266,28 ± 97,34 (32,00-575,00)	274,64 ± 100,21 (52,00-553,00)	259,74 ± 95,00 (32,00-314,51)	0,275
CRP (mg/L)	61,24 ± 74,98 (0,20-317,00)	80,41 ± 83,87 (0,20-317,00)	46,23 ± 63,67 (0,20-314,51)	0,003
D_DIMER (ng/mL)	1127,85 ± 1209,55 (89,00-5620,00)	1966,2 ± 1294,28 (103,00-5620,00)	471,41 ± 566,28 (89,00-3003,00)	0,000
Ferritin (ml/ng)	284,97 ± 351,05 (6,00-1650,00)	359,59 ± 358,15 (9,00-1508,00)	226,54 ± 335,60 (6,00-1650,00)	0,000
Procalcitonın(ng/mL)	3,08 ± 11,74 (00,00−100,00)	4,36 ± 13,69 (0,01−100,00)	2,08 ± 9,91 (00,00-75,00)	0,000

WBC: White Blood Cell, NEU: Neutrophil, LYM: Lymphocyte, NLR: Neutrophil-to-Lymphocyte Ratio.
HCT: Hematocrit, RDW: Red Cell Distribution Width, PLT: Platelet, CRP: C-Reactive Protein.

the severity of AP [19]. We believe that the coexistence of these two conditions (AP and SARS-CoV-2 infection), each of which alone causes increased systemic inflammation, contributed to the worsening of the patient's clinical condition. Likewise, the rate of presence of pleural effusion, which should be taken into account when calculating the BISAP score, might be found high due to COVID-19 pneumonia. Therefore, when the patients were compared according to the BISAP score, we found a higher rate of positive patients with a BISAP score of ≥3.

Pandanaboyana et al. assessed the severity of AP by the Atlanta classification. The authors reported that the mortality rate was high in patients with severe AP, and the severity of AP was a factor affecting mortality [15]. We used the BISAP score to assess the severity of AP. We found that 62.5% of the non-surviving patients had a BISAP score of ≥3, and this was strongly associated with mortality. As is known, AP itself has a mild course in 80% of the cases and recovers with appropriate treatment. However, in the case of severe AP and organ failure,

Table 6
Cut-off values of laboratory parameters to determine COVID-19 positivity

Parameters	AUC (%95)			Cut Off	P	Sensitivity (%)	Specificity (%)
	AUC (%95)	Lower Bound	Upper Bound				
WBC($\times 10^3/\mu L$)	0,726	0,650	0,802	11,29	0,000	68,7	31,1
NEU($\times 10^3/\mu L$)	0,764	0,693	0,836	9,07	0,000	67,5	29,2
N/L	0,804	0,740	0,868	5,87	0,000	71,1	27,4
CRP(mg/L)	0,627	0,546	0,708	31,26	0,003	59,0	40,9
D/DIMER(ng/mL)	0,865	0,810	0,921	627,00	0,000	79,5	17,9
FERRITIN(ml/ng)	0,678	0,602	0,754	191,50	0,000	61,4	30,2
Procalcitonin(ng/mL)	0,723	0,649	0,796	0,16	0,000	66,3	27,4

WBC: White Blood Cell, NEU: Neutrophil, NLR: Neutrophil-to-Lymphocyte Ratio, CRP: C-Reactive Protein.

Table 7
Cut-off values of laboratory parameters to determine mortality

Area Under the Curve							
Test Result Variable(s)	Asymptotic 95% Confidence Interval			Cut Off	p	Sensitivity(%)	Specifity(%)
	AUC(%95)	Lower Bound	Upper Bound				
NLR	0,765	0,657	0,873	10,36	0,000	75,50	26,00
CRP (mg/L)	0,813	0,731	0,896	77,79	0,000	75,00	27,20
D-DİMER (ng/mL)	0,668	0,534	0,802	1203,5	0,027	68,80	31,20
Procalcitonin (ng/mL)	0,659	0,512	0,806	0,22	0,036	68,80	38,70
FERRİTİN (ml/ng)	0,841	0,748	0,934	297,5	0,000	91,30	24,90

NLR: Neutrophil-to-Lymphocyte Ratio, CRP: C-Reactive Protein.

mortality increases up to 30% [26,27]. Among studies conducted with AP patients before the pandemic, the study by Karaali et al. with 343 AP patients established a mortality rate of 4.7% and reported the rate of severe AP as 19.2% [28]. The multicenter study by Yasuda et al. on AP patients found a 30-day mortality rate of 5.4% in 1097 patients [29]. Likewise, the multicenter study by Matta et al. reviewing data from 22 countries reported a mortality rate of 5.7% in Europe, 3.3% in India, 2.3% in Latin America and 0.6% in North America. The rate of severe AP was reported as 9%, except for India [30]. When we evaluate our findings from our study, we see that the rate of severe AP and mortality in COVID-19 positive patients with AP is higher than the rates reported by these studies. When we evaluate the coexistence of AP and other viral infections, we see that there are several publications reporting the coexistence of AP and viral infections until the pandemic, which are, however, case reports or case series. On the other hand, there are no studies regarding the effects of other viral infections on the pancreas and mortality [31]. One reason for this may be that a limited number of patients are affected and the coexistence of these viruses with AP is rare. Therefore, we believe that the increase in disease severity and mortality rate in AP patients with COVID-19 is different from AP with a simple viral infection. Likewise, our findings from our study revealed that the presence of COVID-19 compatible pneumonia had also an effect on mortality. Based on the thoracic CT results, which we evaluated according to the RSNA consensus guidelines, 74.69% of our positive patients had findings compatible with COVID-19 pneumonia. The severity of pneumonia caused by COVID-19 can range from mild consolidations to ARDS. Meng et al. and Li et al. reported that the presence and prevalence of pneumonia increased mortality in patients with COVID-19 [32,33]. Pandanaboyana et al. stated that positive patients had a high risk for ARDS, and the most common organ failure was respiratory failure. The authors reported that mortality in AP patients also occurred primarily due to respiratory failure, and the rate was higher in positive patients [15]. In our study, there was COVID-19compatible pneumonia on CT in 81.3% of the patients who died. It seems that respiratory failure due to COVID-19 also increases pancreatic injury and contributes to mortality. The study by Akarsu et al. evaluating COVID-19 patients classified patients as mild, severe and critical according to the severity of COVID-19 pneumonia. The authors found that AP occurred in COVID-19 patients with severe and critical pneumonia. They reported a higher mortality in the pancreatitis group than in the non-pancreatitis group [34]. Considering the greater severity and mortality of AP in positive patients than in negative patients, we believe that patients diagnosed with AP during the pandemic should be examined not only for COVID-19 but also for the presence of associated pneumonia. Our findings further show that severity and mortality are affected by respiratory problems and inflammatory processes caused by COVID-19. Pandanaboyana et al. addressed this issue in their study and reported increased mortality in patients with severe AP and ARDS, which is consistent with our findings [15].

The common finding of studies on COVID-19 is that increased inflammatory response and cytokines are involved in the pathogenesis of the disease. We also evaluated inflammatory markers in our study. We found that CRP, Ferritin, D-DIMER, PCT, and NLR from laboratory data of the patients had an effect on patient mortality. CRP, D-DIMER, Ferritin, Procalcitonin, WBC, and NLR are inflammatory parameters that have been associated with disease severity and mortality in COVID-19 patients [35,36]. Our study established that NLR and D-dimer values, in particular, differed between COVID-19 positive and negative patients. However, the sensitivity and specificity assessment revealed low sensitivity and specificity for all parameters. Pandanaboyana et al., similar to our study, compared only LDH and ferritin from the laboratory values of COVID-19 positive and negative patients and found both parameters to be significantly different. However, the authors did not evaluate sensitivity and specificity [15]. Comparing COVID-19 patients with and without AP, Akarsu et al. identified a statistically significant difference in CRP, WBC, LNR (lymphocyte-to-neutrophil ratio), HCT ferritin values between the groups [34]. Our study is different from this study because all of our patients were diagnosed with AP. CRP, NLR, and NEU are well-established and prognostic parameters for mortality in patients with AP [37,38]. It is known that AP itself is also a process that induces inflammation [3]. We believe that this was the reason why we established low sensitivity and specificity for laboratory values in discriminating between COVID-19 positive and negative patients. However, we can say that the inflammatory processes were more severe in AP accompanied by SARS-CoV-2 infection than in AP without SARS-CoV-2 infection.

Although etiology of AP, CCI score, COVID-19 positivity, and treatment methods as other factors affecting mortality were found statistically significant, the effect sizes were low. Other parameters associated with mortality were the length of hospital stay and the need for intensive care unit admission. In our study, the hospital stay was longer, and the intensive care unit admission rate was higher in positive patients than in negative patients. Based on this finding, we can say that AP patients with COVID-19 need more intensive care hospitalization and stay in hospital for longer periods. Our findings are consistent with those of Pandanaboyana et al. and Inamdar et al. [14,15]. As especially emphasized by Pandanaboyana et al., we believe that this was resulted from the respiratory failure due to COVID-19 and the associated clinical worsening.

Unlike the study by Pandanaboyana et al., the present study found no difference in AP-related complications between positive and negative patients. The study by Pandanaboyana et al. was multicenter, and as stated by the authors, some centers from which data were collected were non-specialist pancreatic centers [15]. Our hospital is the largest gastroenterology center in our region and actively provides 24/7-service. We can say that the rate of AP-related complications was low even when all patients were considered. There was no difference between positive and negative patients due to the quick assessment of patients admitted to the emergency department and appropriate interventions in the early period by the gastroenterology unit.

In their paper evaluating the coexistence of severe AP and COVID-19, Hegyi et al. indicated that SARS-CoV-2 resulted in high lipase activity in the absence of acute pancreatitis findings. According to the authors, lipase causes hydrolysis in adipose tissue and the released non-esterified fatty acids stimulate inflammation, resulting in the cytokine storm and multisystemic disease. AP itself is a condition with an elevated level of lipase. Hegyi et al. stated that in the case of coexistence of AP and COVID-19, the lipase level would elevate further and the inflammation induced by this elevation might be even more severe. This helps to explain the severe inflammation and increased disease severity that occur in the coexistence of AP and COVID-19. These patients may require the administration of anti-inflammatory therapy in addition to AP treatment. Administration of calcium and/or albumin, which binds fatty acids, is recommended for these patients [39]. In addition, systems for the removal of cytokines from the blood, such as Cytosorb, have been tried in severe patients [40]. Although not recommended yet as a treatment option, agents such as avoralstat, which were shown to prevent the SARS-CoV-2 entry into the cell in animal experiments, were suggested to reduce the disease severity and mortality by preventing the entry of the virus into both the respiratory tract and the pancreas [41].

5. Conclusion

In conclusion, we do not know whether patients first developed AP or COVID-19. Therefore, it is still unclear whether AP is caused by COVID-19 or the inflammatory process occurring in the course of the disease. In addition, severe AP can increase susceptibility to COVID-19 or change the course of COVID-19. In both cases, the severity and mortality increase in patients with both AP and COVID-19. This rate increases even more in the presence of COVID-19-associated pneumonia. We believe that new strategies should be developed for the follow-up and treatment of patients with both these conditions.

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