Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Lipase elevation on admission predicts worse clinical outcomes in patients with COVID-19

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ABSTRACT

Background and objectives: Hyperlipasemia is highly prevalent among coronavirus disease 2019 (COVID-19) patients. The aim of this study was to assess the effect of lipase activity, measured at the time of admission, on the clinical course and mortality in COVID-19 patients.
Methods: The population of this study comprised 12,139 patients who were hospitalized due to COVID-19 between June 2020 and June 2021 in a pandemic hospital. Of these, 8819 patients were excluded from the study due to missing data, four patients were excluded due to a diagnosis of acute pancreatitis (according to the revised Atlanta criteria), and 72 patients were excluded due to alcohol use or having a history of chronic pancreatitis. The final study sample consisted of the remaining 3244 COVID-19 patients. Laboratory results, intensive care unit (ICU) follow-up periods, the need for mechanical ventilation, and mortality rates were compared between the normal lipase activity and high lipase activity groups.
Results: There were 968 (29.8%) patients with high lipase activity at the time of admission. The rate of ICU admission was 36.1% vs. 9.9% ($p < 0.001$), mechanical ventilation requirement rates were 33.7% vs. 8.3% ($p < 0.001$), and mortality rates were as 24.6% vs. 6.4% ($p < 0.001$) in the high lipase activity group compared to the normal lipase activity group. Multivariate regression analysis revealed that high lipase activity was an independent factor in predicting mortality in hospitalized COVID-19 patients (odds ratio [OR]: 3.191, $p < 0.001$).
Conclusion: Elevated lipase activity without acute pancreatitis at the time of admission in COVID-19 patients was determined as an independent predictor of poor prognosis.

1. Introduction

Coronavirus disease 2019 (COVID-19), which was declared a pandemic on March 11, 2020, by the World Health Organization (WHO), is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and it continues to affect the world [1]. To date, more than 274 million people have been diagnosed with COVID-19, of whom 5.3 million have died [2].

COVID-19 was thought to be limited to the respiratory system in the initial stages of the pandemic. However, new evidence has emerged over time indicating that the infection may involve other systems as well [3]. The most crucial factor in the multi-organ involvement of COVID-19 is the abundant expression of the angiotensin converting enzyme-2 (ACE-2) receptor in endothelial cells [4]. Early in the pandemic, the prognosis of COVID-19 in patients was being determined according to their clinical status, peripheral oxygen saturation (SpO2) levels, and concomitant comorbidities [5]. However, this approach has some drawbacks. In some cases, it gives rise to unnecessary intensive care unit (ICU) admissions due to incorrect triage, and it does not enable timely intervention in patients who suddenly deteriorate and must be transferred to the ICU. Considering the spread of the disease, the accurate and early identification of patients and timely intervention have become even more important [6].

Therefore, several inflammation-based laboratory parameters, such as C-reactive protein (CRP), leukocyte, neutrophil, D-dimer, and ferritin values, have been used together with clinical findings to predict poor prognosis in COVID-19 patients at the time of diagnosis [7]. However, it was determined that several non-inflammatory laboratory parameters were also elevated in

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COVID-19 patients, one of which is lipase activity. The expression of the ACE-2 receptor in pancreatic islet cells and exocrine glands and the higher expression of this receptor in pancreatic cells than in pulmonary cells suggest that it constitutes a potential target for pancreatic damage [8].

Studies in the literature reported high lipase activity in COVID-19 patients without acute pancreatitis. Nevertheless, the effect of lipase activity on mortality has not yet been elucidated [9]. The COVID-19 pandemic may be managed only if the spread of the disease is prevented and if appropriate treatment methods are administered to the patients who contract the disease despite the measures implemented to prevent its spread. This would only be possible through the establishment of an early diagnosis or prognosis prediction [10]. The aim of this study was to evaluate the effect of lipase activity at the time of admission on the clinical course and mortality rates of patients who were referred with a pre-diagnosis of COVID-19 to the pandemic hospital used in this study, one of the largest pandemic centers in Turkey.

2. Methods

2.1. Patient selection

The population of this retrospective, single-center study comprised 12,139 patients who were hospitalized due to COVID-19 between June 2020 and June 2021 in a pandemic hospital, which was built in over a brief period in Istanbul, Turkey, solely to manage COVID-19 patients, and who were older than 18 years at the time of admission. The final diagnosis of the patients was made by a real-time polymerase chain reaction (PCR) test conducted using a nasopharyngeal swab. All the patients were treated in accordance with the recommendations of the national adult patient treatment guidelines [11]. All patients were followed up until discharge or mortality. Demographic characteristics, medical history, and laboratory data of the patients who tested positive for COVID-19 based on the real-time PCR test at the time of admission were obtained from hospital records. Accordingly, white blood cell count (WBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), amylase, lipase, total bilirubin, fibrinogen, D-dimer, and CRP values of the patients, which were measured upon admission to the hospital, were recorded. Of these patients, 8819 were excluded from the study due to missing data. Abdominal computed tomography (CT) and/or ultrasonography (USG) were performed in 173 patients who had lipase activity more than three times the upper limit of normal and/or abdominal pain. Radiological imaging revealed edematous pancreatic enlargement in three patients and peripancreatic edema and fluid collection in one patient. Thus, four patients were excluded from the study due to being diagnosed with acute pancreatitis, as they met two of the three criteria set forth in the Revised Atlanta Classification of Acute Pancreatitis. These criteria are: having characteristic upper abdominal pain, elevated lipase activity more than three times the upper limit of normal, and the presence of radiological (CT or USG) findings that support the diagnosis of acute pancreatitis. An additional 72 patients were excluded from the study due to alcohol use or having a history of chronic pancreatitis. The remaining 3244 COVID-19 patients constituted the study sample (Fig. 1). The patients included in the study sample were divided into two groups: patients with normal lipase activity and patients with high lipase activity. Patients with lipase values of >60 U/L were deemed to have high or elevated lipase activity or hyperlipasemia. The laboratory results, the need for ICU admission, the need for mechanical ventilation (intubation), the duration of ICU follow-up, and mortality rates were compared between the two groups.

2.2. Statistical analysis

Statistical analyses were conducted using the SPSS 20 (Statistical Package for Social Sciences for Windows, Version 20.0, IBM Corp., Armonk, NY, U.S., 2011) software package. Continuous data were expressed using mean ± standard deviation values, whereas the categorical data were expressed using percentage values. Fisher's exact test and the Student's t-test were used for categorical and numerical variables, respectively, to evaluate the statistical differences between the baseline characteristics of the patients with normal and high lipase activity and the patients in the survivor and mortality groups. Because the dependent variable in the mortality group was categorical, the multivariate binary logistic regression model was used for the respective statistical analyses. The independent samples *t*-test was used to determine whether there was a difference between the survivor and mortality groups in terms of the mean values of the independent variables. Consequently, no significant difference was found between the survivor and mortality groups in terms of AST, ALT, GGT, ALP, and glucose values. Therefore, these variables were not included in the logistic regression model. Multivariate logistic regression analyses were performed to calculate the odds ratio (OR) values to assess any correlation between lipase activity and mortality. Probability (p) values of <0.05 were deemed to indicate statistical significance.

The protocol of this study was approved by the Ethics Committee of the Prof. Dr. Ilhan Varank Training and Research Hospital of the University of Health Sciences with the decision number 2021/196. This study was carried out in line with the principles of the Declaration of Helsinki.

3. Results

In total, 12,139 patients diagnosed with COVID-19 were screened, and 3244 patients who met the inclusion criteria were included in the study. Of these 3244 patients, 1896 (58.4%) were male. The mean ages of the male and female patients were calculated as 59.5 ± 16 and 63 ± 17.1 years, respectively. The mean ages of the patients in the normal and high lipase activity groups were calculated as 60.91 ± 16.62 and 61.9 ± 16.34 years, respectively ($p = 0.806$). There were 968 (29.8%) patients in the group with high lipase activity at the time of admission. In 101 (3.1%) of these patients, lipase activity was more than three times the upper limit of normal. There was no significant difference between the groups with normal and high lipase activity in terms of complaints at admission ($p = 0.727$). The most common complaint was fever, which was followed by cough. The symptoms were observed to have intensified over a period of 1–2 days before admission. Clinical characteristics of the study groups are given in Table 1.

Amylase ($p < 0.001$), AST ($p = 0.025$), ALT ($p < 0.001$), GGT ($p < 0.001$), LDH ($p = 0.004$), total bilirubin ($p < 0.001$), leukocyte ($p < 0.001$), CRP ($p < 0.001$), and fibrinogen ($p < 0.001$) values were significantly higher in the group with high lipase activity than in the group with normal lipase activity (Table 2). In addition, the length of hospital stay was significantly higher in the group with high lipase activity than in the group with normal lipase activity (10.6 days vs. 8.96 days, $p < 0.001$). Further, the rate of ICU admission ($p < 0.001$), the need for mechanical ventilation ($p < 0.001$), and the mortality rate ($p < 0.001$) were significantly higher in the group with high lipase activity than in the group with normal lipase activity (Table 1). A multivariate logistic regression analysis revealed a weak significant relationship between mortality and high amylase activity (OR: 1.015, $p < 0.001$) and a strong and significant relationship between mortality and male gender (OR: 2.163, $p < 0.001$), age (>65 years) (OR:1.547, $p = 0.004$), and high lipase activity (OR: 3.191, $p < 0.001$) (Table 3).

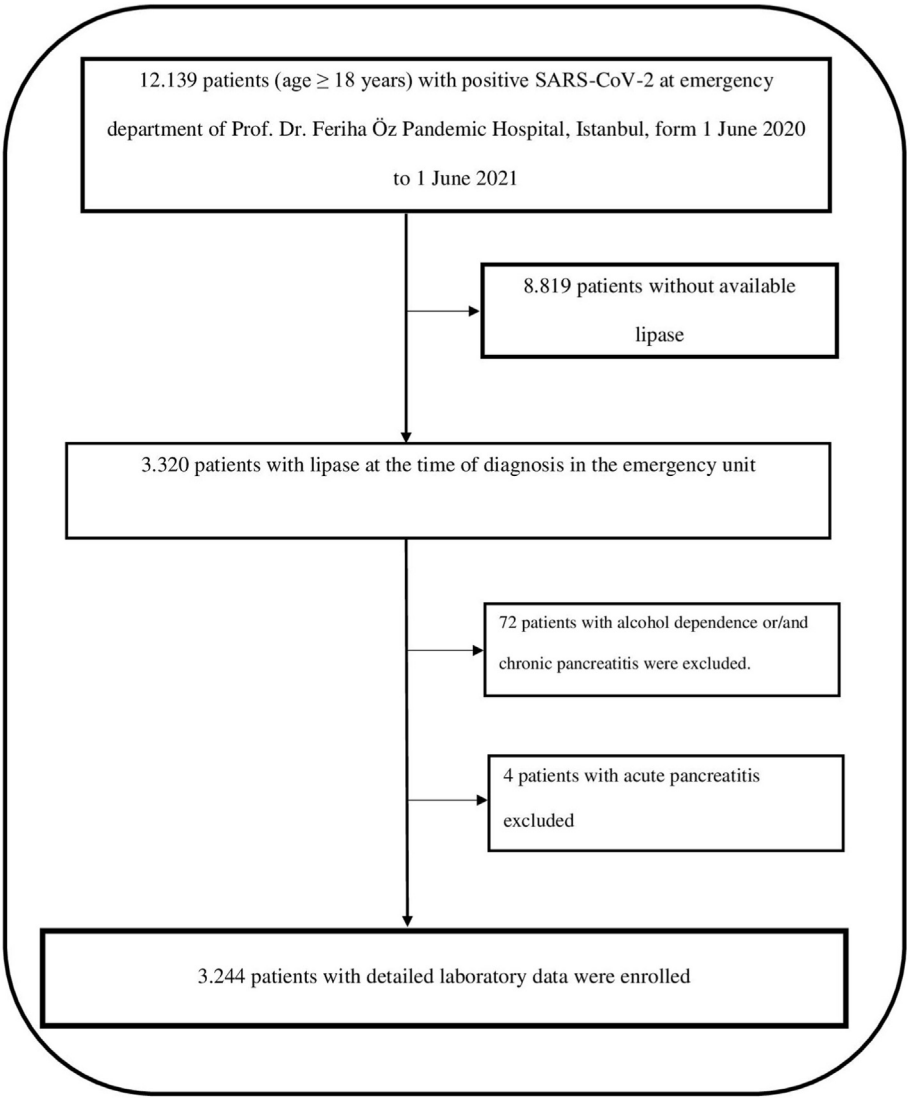

Fig. 1. Flowchart of the study.

Table 1
Charasteristics of study population.

		Normal Lipase		Elevated Lipase		*p*
		n	%	n	%	
Gender	Male	1301	57.20%	595	61.50%	0.806
	Female	975	42.80%	373	38.50%	
Complaint	Fever	805	35.40%	327	33.80%	0.727
	Cough	633	27.80%	263	27.20%	
	Myalgia	458	20.10%	174	18.00%	
	Diarrhea	216	9.50%	94	9.70%	
	Dyspnea	81	3.60%	45	4.60%	
	Headache, loss of taste and smell	48	2.10%	25	2.60%	
	Stomach ache	35	1.50%	40	4.10%	
Hospital course	ICU +	226	9.90%	349	36.10%	<0.001*
	ICU -	2050	90.10%	619	63.90%	
Mechanical ventilation	MV+	189	8.30%	326	33.70%	<0.001*
	MV-	2087	91.70%	642	66.30%	
Mortality	Deceased	146	6.40%	238	24.60%	<0.001*
	Survivors	2130	93.60%	730	75.40%	

*$p < 0.05$ is accepted as statistical significance level.
ICU: intensive care unit, MV: mechanical ventilation.

Table 2
Comparison of laboratory values of normal lipase and elevated lipase groups in COVID-19 patients.

	Normal Lipase (n = 2276)	Elevated Lipase (n = 968)	*p*
Glucose (mg/dL)	157 ± 112	154 ± 111	0.498
Amylase (U/L)	59 ± 24	83 ± 36	<0.001*
Lipase (U/L)	32 ± 15	105 ± 46	<0.001*
AST (U/L)	49 ± 35	66 ± 43	0.025*
ALT (U/L)	51 ± 43	58 ± 59	<0.001*
ALP (U/L)	76 ± 52	77 ± 57	0.594
GGT (U/L)	52 ± 48	61 ± 59	<0.001*
LDH (U/L)	357 ± 356	393 ± 224	0.004*
Total biluribin (mg/dL)	0.9 ± 0.5	1.1 ± 0.8	<0.001*
Leukocyte (10^3/μL)	8.1 ± 2.8	9.5 ± 4.7	<0.001*
Crp (mg/L)	17 ± 17	28 ± 29	<0.001*
D-dimer (mg/L)	4.1 ± 3.1	4.6 ± 2.9	0.596
Fibrinogen (mg/dL)	430 ± 231	462 ± 249	<0.001*

*p < 0.05 is accepted as statistically significant.
The expression '+/−' is presented as standard deviation (SD).
ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, CRP:C-reactive protein, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase.

Table 3
Multivariate logistic regression for mortality in COVID-19 patients.

	OR	95% CI		*p*
		Lower	Upper	
Age (>65)	1.547	1.149	2.082	0.004*
Gender (Male)	2.163	1.580	2.963	<0.001*
Amylase (U/L)	1.015	1.010	1.020	<0.001*
Lipase (U/L)	3.191	2.320	4.390	<0.001*
Total Biluribin (mg/dL)	0.737	0.606	0.896	0.002*
LDH (U/L)	0.999	0.999	1.000	<0.001*
CRP (mg/L)	0.956	0.951	0.961	<0.001*
Leukocyte (103/μL)	0.729	0.689	0.770	<0.001*
Fibrinogen (mg/dL)	1.000	1.000	1.001	0.550
D-dimer (mg/L)	1.003	0.995	1.011	0.513

*$p < 0.05$ is accepted as statistical significance level.
CI: confidence interval, CRP: C-reactive protein, LDH: lactate dehydrogenase, OR: odds ratio.

4. Discussion

Early diagnosis and timely treatment of COVID-19 is of critical importance, particularly in severe cases. Some studies in the literature addressed factors that can be used to predict poor outcome in patients, but the relationship between elevated lipase activity and prognosis in patients with COVID-19 had not yet been elaborated.

In the literature, it has been suggested that severe AP and severe COVID-19 disease have similar mechanisms in the process leading to multisystemic organ failure. In addition, severe AP and severe COVID-19 disease have common risk factors, such as obesity, high lipase activity, hypoalbuminemia, and hypocalcemia [12,13]. Autopsy studies have shown pancreatic involvement and fat necrosis in COVID-19 patients without symptoms of pancreatitis. The autopsy results of 11 COVID-19 patients from Austria revealed that four patients had focal pancreatitis [14]. In another study, the autopsies of eight patients who died due to COVID-19 revealed that two patients had microscopic pancreatitis [15]. Although pancreatic damage was seen at a high rate in autopsy series of patients who died due to COVID-19, the AP rate was reported as lower in clinical studies of high-volume COVID-19 patients.

Four (0.12%) patients diagnosed with acute pancreatitis among the patients hospitalized due to COVID-19 were not included in the study. In comparison, Inamdar et al. and Pezzili et al. reported the prevalence of acute pancreatitis among patients hospitalized due to COVID-19 as 0.27% and 2%, respectively [16,17]. The relatively lower prevalence of acute pancreatitis found in this study might be attributed to the fact that the study population comprised patients who presented with primary COVID-19 complaints to a pandemic hospital, one specifically for patients diagnosed/prediagnosed with COVID-19.

In a meta-analysis of 60 studies including more than 50,000 patients, it was concluded that elderly adult patients had a higher risk of mortality than younger patients [18]. In another meta-analysis consisting of 49 studies, advanced age and male gender were reported among the determinants that can be used to identify the risk of in-hospital mortality in COVID-19 patients [19].

During the early days of the pandemic, mild to moderate pancreatic injury was deemed a clinically significant finding in COVID-19 patients [20]. Later, it was stated in several studies that elevated amylase and/or lipase activity did not necessarily indicate a pancreatic injury in COVID-19 patients and that increased enzymes might be an indicator of other clinical conditions [21]. In one of these studies, Rasch et al. determined that elevated lipase activity without typical signs of acute pancreatitis was a frequent finding associated with acute respiratory distress syndrome (ARDS) in severe COVID-19 cases [22]. In another study, Ramsey et al. determined that elevated pancreatic enzyme activity was relatively common among patients hospitalized due to COVID-19, but this rarely signified a clinical diagnosis of acute pancreatitis. It was stated in another study that elevated serum lipase activity may reflect the overall disease severity in COVID-19 patients [23]. The findings of Singh et al. support this hypothesis in that they determined, as a result of their population-based, multicenter, retrospective cohort study, that elevated serum lipase activity was associated with worse clinical outcomes, even in the absence of acute pancreatitis [24]. Recently, Benias et al. reported that COVID-19 patients with lipase activity more than three times the upper limit of normal and with asymptomatic hyperlipasemia had generally worse outcomes than those with pancreatitis [25]. In another multicenter study, it was reported that 429 (43%) of 992 COVID-19 patients had hyperlipasemia and that the length of hospital stay, the rate of ICU admission, the need for mechanical ventilation, and the rate of mortality were all significantly higher in COVID-19 patients with hyperlipasemia than in COVID-19 patients with normal lipase activity [26]. Nevertheless, in the aforementioned study, the lipase activity in each COVID-19 patient included in the study was measured more than once, and the highest lipase activity was taken as the reference value. Barlass et al. also associated the elevated lipase activity with worse disease outcomes [9], but their study had limitations in that the patients with acute pancreatitis in the hyperlipasemia group were not assessed, and the elevated lipase enzyme-related risk factors associated with poor outcomes in COVID-19 patients were not addressed. In comparison, in this study, the need to be transferred to ICU, the need for mechanical ventilation, and the mortality rate were significantly higher in the group with high lipase activity than in the group with normal lipase activity. Accordingly, it was determined that high lipase activity predicts mortality in hospitalized COVID-19 patients. In another study including 55 COVID-19 patients, patients with elevated pancreatic lipase activity (48.2%) were found to have a higher rate of mortality, higher need for mechanical ventilation, and higher rate of kidney injury compared to patients with normal pancreatic enzyme activity [27]. This rate is higher than the respective rate reported in this study, which makes sense given that the sample of the aforementioned study comprised only patients hospitalized in the ICU. Another reason for the relatively higher prevalence of hyperlipasemia in the aforementioned study compared to this study might be that the highest lipase activity measured during ICU stay was taken as the reference value, instead

of the lipase activity measured at admission, which was taken as the reference value in this study.

The relevant data available in the literature are contradictory. For example, Caruso et al. reported elevated lipase activity in one-third of the 1092 patients hospitalized due to COVID-19 included in their study, yet they could not establish the clinical significance of this finding, as they could not find any relationship between the elevated lipase activity and the prognosis [28]. Similarly, in a retrospective cohort study of 71 COVID-19 patients, it was reported that hyperlipasemia was not associated with poor outcomes in cases without acute pancreatitis [29].

ALT and AST activity in patients with elevated lipase activity were also found to be significantly higher than those in patients with normal lipase activity. In fact, it was reported in a study conducted in Italy that higher liver function test results were associated with a more severe disease course in COVID-19 patients [6]. However, it was reported in the aforementioned study that ALT activity had a weak significant relationship with mortality, whereas AST activity did not have any significant relationship with mortality at all in COVID-19 patients. In comparison, in this study, although AST and ALT activity were found to be higher in the group with high lipase activity than in the group with normal lipase activity, there was no significant difference between the groups in terms of mortality. Hence, AST and ALT activity were not included in the statistical analyses conducted using the multiple logistic regression model. In another study including 269 COVID-19 patients, GGT was reported as one of the independent factors predicting ICU admission and mortality [30]. In comparison, in this study, GGT values in the group with high lipase activity were significantly higher than in the group with normal lipase activity; however, GGT was not one of the independent factors that was determined to predict mortality successfully in this patient population. In a study including 1378 COVID-19 patients, it was reported that high amylase activity was associated with severe disease outcomes [31]. In comparison, in this study, a weak correlation was found between high amylase activity measured at admission and mortality. Herold et al. reported that CRP values at admission successfully predicted the need for mechanical ventilation in patients with COVID-19 [32], whereas Zeng et al. reported that serum D-dimer values at admission successfully predicted the severity of COVID-19 disease [33]. In comparison, in this study, the CRP values in the group with high lipase activity were significantly higher than in the group with normal lipase activity, while the D-dimer values did not differ significantly between the two groups.

There are several meta-analyses available in the literature on the prognostic value of different parameters, including neutrophil, monocyte, eosinophil, hemoglobin, red blood cell distribution width, lymphocyte, thrombocyte, procalcitonin, albumin, serum sodium, blood urea nitrogen, creatinine, erythrocyte sedimentation rate, prothrombin time, and pre-COVID period HbA1c (hemoglobin A1c) [34–39].

One of the strengths of this study is its large sample size. In addition, contrary to other studies that have addressed the relationship between increased lipase activity and disease outcomes in COVID-19 patients, this study is the first to date in which elevated lipase activity measured at admission (not peak lipase activity measured during the disease course) in COVID-19 patients without acute pancreatitis was assessed. Using the lipase activity measured upon admission as a reference is important, as early prognosis predictions may allow physicians to plan necessary interventions as soon as possible. Apart from its strengths, there were also some limitations to this study. The primary limitation is that it was designed as a retrospective, single-center study, and some data might have been missed due to this design. Second, the fact that such conditions as chronic kidney failure; hemodialysis; the presence of macrolipase; intra-abdominal pathologies originating from the stomach, intestine, or hepatobiliary system; and the use of some medications, such as dipeptidyl peptidase inhibitors, sitagliptin, saxagliptin, etc. Might have also led to elevated lipase activity in the absence of acute pancreatitis could not be factored into the analyses, as it was outside the scope of this study [40].

In conclusion, elevated lipase activity without acute pancreatitis upon admission in COVID-19 patients was determined as an independent predictor of poor prognosis, prognosticating the need to be transferred to the ICU and the need for mechanical ventilation, as well as mortality. Therefore, the lipase test, which is an easily accessible test in the emergency departments of most hospitals, may be used as a tool to predict prognosis in COVID-19 patients at the time of admission, along with other tests.

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Author's contribution

MK study conception and design, development of survey, manuscript writing, statistical analysis. TD manuscript review and editing.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki and approved by the Health Science University, Prof. Dr. Ilhan Varank Training and Research Hospital (Decision nu:2021/196).

Declaration of competing interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2022.04.012.

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