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Retrospective Evaluation of the Frequency of Acute Pancreatitis in Adult Hospitalized Patients with COVID-19 Infection

COVID-19 Enfeksiyonu ile Yatarak Takip Edilen Erişkin Hastalarda Akut Pankreatit Sıklığının Retrospektif Olarak Değerlendirilmesi

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Abstract

Introduction: Data on the relationship between Coronavirus disease-2019 (COVID-19) and acute pancreatitis are limited. This study aimed to investigate the possible role of COVID-19 in the etiology of acute pancreatitis in a tertiary-care educational university hospital by retrospectively evaluating the incidence of acute pancreatitis in adult hospitalized patients with COVID-19.

Materials and Methods: Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR)-positive adult inpatients from March 15, 2020, to February 1, 2021, constituted the study group in our hospital. This cohort was analyzed for acute pancreatitis criteria, including acute abdominal pain, increased amylase and/or lipase more than three times the normal value, and radiological finding supporting the disease. Patients who met at least two of the acute pancreatitis diagnostic criteria were determined, and those who met the criteria during or after SARS-CoV-2 PCR positivity detection were included in the study. These patients were further analyzed for COVID-19-related data and pancreatitis severity status.

Results: Our hospital had 1227 inpatients with COVID-19 diagnosis in one year. A total of four cases met the inclusion criteria. Acute pancreatitis rates were detected at 0.3% and 1.07% for all cohorts (n=1227) and the pancreatic enzyme-tested group (n=372), respectively. Of these four patients, two (50%) were females (50%) and the mean age was 70.7 (range: 64-79) years. There was no correlation between COVID-19 pneumonia and pancreatitis severity scores, including Ranson, Acute Physiologic Assessment and Chronic Health Evaluation 2, and modified computed tomography severity scores.

Conclusion: COVID-19 is a rare risk factor for acute pancreatitis and did not affect the pancreatitis severity or mortality in our cohort.

Keywords: COVID-19, acute pancreatitis, SARS-CoV-2

Öz

Giriş: Koronavirüs hastalığı-2019 (COVID-19) ile akut pankreatit arasındaki ilişki hakkında sınırlı veri bulunmaktadır. Burada üçüncü basamak bir üniversite hastanesinde akut pankreatit etiyolojisinde COVID-19'un olası rolünün araştırılması amaçlanmıştır. Bu amaçla, COVID-19 tanısı ile hastanede yatan erişkin hastalarda akut pankreatit insidansı geriye dönük olarak değerlendirildi.

Gereç ve Yöntem: Çalışma grubunu hastanemizde 15 Mart 2020-1 Şubat 2021 tarihleri arasında yatan Şiddetli akut solunum yolu sendromu-Koronavirüs-2 (SARS-CoV-2) polimeraz zincir reaksiyonu (PZR) pozitif erişkin hastalar oluşturdu. Bu kohort, akut pankreatit kriterleri için analiz

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edildi. Akut pankreatit tanı kriterlerinden en az ikisini (akut karın ağrısı, normal değerin üç katından fazla amilaz ve/veya lipaz artışı, hastalığı destekleyen radyolojik bulgu) karşılayan hastalar belirlendi. SARS-CoV-2 PCR pozitifliği tespiti sırasında veya sonrasında akut pankreatit kriterlerini karşılayan hastalar çalışmaya dahil edildi. Bu hastalar, COVID-19 ile ilgili veriler ve pankreatit şiddeti açısından ileri analize alındı.
Bulgular: Hastanemizde bir yıl içinde COVID-19 tanısı ile yatan 1.227 hasta vardı. Toplam dört olgu dahil edilme kriterlerini karşıladı. Akut pankreatit oranı, kohortun tamamı (n=1.227) ve pankreas enzimi test edilen grup (n=372) için sırasıyla %0,3 ve %1,07 olarak tespit edildi. Bu dört hastanın ikisi (%50) kadın (%50) ve yaş ortalaması 70,7 (minimum=64, maksimum=79) idi. COVID-19 pnömoni skoru ile Ranson, APACHE 2 ve modifiye CT şiddet skorları dahil olmak üzere pankreatit şiddet skorları arasında bir korelasyon yoktu.
Sonuç: COVID-19, akut pankreatit için nadir bir risk faktörüdür ve kohortumuzda pankreatit şiddetini veya mortalitesini etkilememiştir.
Anahtar Kelimeler: COVID-19, akut pankreatit, SARS-CoV-2

Introduction

Coronavirus disease-2019 (COVID-19) is a serious worldwide epidemic that emerged in December 2019 in Wuhan, China. Over 430 million cases and over 5.9 million deaths were reported as of February 2022[1].

Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) is the causative agent of COVID-19. It enters the host cell using the angiotensin-converting enzyme-2 (ACE-2) and Transmembrane Serine Protease 2 receptors. Hence, the virus may cause pathology in all organs that express these receptors. Intestinal epithelial infection was shown in many publications. The virus has been isolated in the feces[2]. Pancreatic ductal, acinar, and islet cells also express ACE-2 receptors. Thus, the direct cytopathic effect of the virus or indirect systemic inflammation may cause pancreatic enzyme elevation or organ damage in some COVID-19 cases. SARS-CoV-2 was also isolated from the pancreatic pseudocyst fluid of a patient with acute pancreatitis[3]. Acute viral pancreatitis due to etiological agents, such as mumps, measles, coxsackie viruses, Epstein-Barr virus, and hepatitis A viruses, were described in the literature[4].

Accompanying polymerase chain reaction (PCR) positivity had increased mortality and morbidity in a study comparing cases with acute pancreatitis in terms of SARS-CoV-2 PCR positivity[5].

This study aimed to investigate the possible role of COVID-19 in the etiology of acute pancreatitis in a tertiary-care educational university hospital by retrospectively evaluating the incidence of acute pancreatitis in adult hospitalized patients with COVID-19.

Materials and Methods

Our setting is the largest hospital in the region with 1800+ beds and has been actively serving during the pandemic period.

Adult patients that received inpatient treatment due to COVID-19 at our setting from March 15, 2020, to February 1, 2021, constituted the study group.

Inclusion criteria were as follows:

a) Those who are 18 years of age or older and were inpatients with SARS-CoV-2 PCR positivity.

b) Patient information and consent form signing. All COVID-19 inpatients were screened in terms of biochemical and radiological [computed tomography (CT) and ultrasonography] acute pancreatitis criteria.

c) Patients who meet at least two of the acute pancreatitis diagnostic criteria, including acute abdominal pain, increased amylase and/or lipase more than 3 times the normal value, and radiological finding supporting the disease (CT or ultrasonography), were considered to have acute pancreatitis[6].

d) Patients who met the criteria for acute pancreatitis during or after SARS-CoV-2 PCR positive detection were included.

Patients diagnosed with acute pancreatitis were further analyzed in terms of COVID-19-associated data. All patient information was retrospectively retrieved from the electronic patient files. Study parameters included patient demographics, chronic diseases, medications, surgical operation history, medical family history, complaints during the presentation, clinical course, biochemical data, and imaging reports. Besides, the length of hospital and intensive care unit stay, as well as the need for intubation and prognosis, were determined from their files.

COVID-19 was diagnosed based on positive detection of nucleic acid amplification test in nasopharyngeal swab samples (Coyote Biosciences, San Jose, CA, USA) and radiological findings.

Serum amylase and lipase levels were studied with an autoanalyzer in peripheral serum samples using standard kits. Repeated measurements were recorded in chronological order. Furthermore, biochemical analyses of all inpatient COVID-19 cases with amylase, lipase request or pre-diagnosis of pancreatitis were chronologically examined.

The COVID-19 pneumonia severity was assessed using a chest CT scoring system, wherein each lobe was given a score based on the following: score of 0: no involvement; 1: <5%; 2: 5-25%; 3: 26-49%; 4: 50-75%; and 5, >75% lobar involvement[7,8].

All CT examinations were performed using a 160-slice-CT scanner (Aquilion Prime, Canon Medical Systems, Tochigi, Japan). Chest CT images were obtained using the following parameters; 120 kVp, 100-200 mA, 80×0.5 mm collimation, and reconstructed at 0.5 mm slice thickness with a sharp reconstruction kernel.

Abdominal CT scans were obtained with intravenous non-ionic contrast material administration unless with renal impairment or contrast allergy contraindications. Arterial and portal venous phase images were acquired. Images were transferred and reviewed in the picture archiving and communication system (Sectra IDS7, Linköping, Sweden).

Ranson's criteria and the second version of the Acute Physiologic Assessment and Chronic Health Evaluation 2 (APACHE 2) scores were used for pancreatitis severity classification[9,10]. The 1991 consensus guidelines, as well as Revised Atlanta criteria, were applied to classify pancreatitis severity and complications[6].

The study was approved by the Ministry of Health with the number 2021-02-18T13_06_48 and the Ege University Hospital Ethics Committee with the number E-99166796-0.50.06.04-124496, date: 01.04.2021.

Statistical Analysis

The chi-squared test, Student's t-test, and Spearman's correlation test were used whenever required for statistical comparison. Normally, distributed continuous variables are reported as mean±standard deviation. P values of <0.05 were accepted as statistically significant. Statistical Package for the Social Sciences (SPSS) version 20.00 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

The study consisted of 1.227 patients with SARS-CoV-2 PCR positivity who were followed up in our hospital from March 2020 to April 2021. Amylase and/or lipase were tested at least once in the follow-up of 372 (30.3%) patients, and 13 patients with three times the normal or higher amylase (N: 28-100 U/L) and/or lipase (N: <60 U/L) values, which are among the acute pancreatitis diagnostic criteria, were retrospectively analyzed. Both amylase and lipase values were high in seven, isolated amylase value was increased in three, and isolated lipase value was increased in three of these patients. Additionally, 168 of 372 (45.2%) patients had at least one day of intensive care unit follow-up due to COVID-19.

The presence of abdominal pain and radiological imaging findings supporting the disease were re-evaluated in 13 patients with high amylase and lipase levels. Acute pancreatitis was excluded after alternative diagnoses, such as cholecystitis, mesenteric ischemia, acute liver failure, and gastric perforation, in six patients.

The study population was re-screened in terms of patients that did not meet the amylase and/or lipase elevation criteria for acute pancreatitis but could meet the other two criteria. Hence, four more patients who met the diagnostic criteria were further detected.

All patients had both acute pancreatitis and SARS-CoV-2 PCR positivity. However, seven of these patients were excluded from the study because they developed SARS-CoV-2 PCR positivity after hospital follow-up due to acute pancreatitis. The clinics of these patients did not follow the chronological order. The other four patients met the acute pancreatitis criteria while receiving COVID-19 treatment in the hospital. The acute pancreatitis rate was 0.3% and 1.07% for all cohorts (n=1227) and the pancreatic enzyme-tested group (n=372), respectively.

Of these four patients, two (50%) were female and the mean age was 70.7 (range: 64-79) years. All patients had positive SARS-CoV-2 PCR tests. Thoracic CT of only one patient was compatible with COVID-19. Table 1 shows all clinical findings and biochemical results. COVID-19 severity, pancreatitis severity, Ranson, APACHE 2, and Atlanta scores of all cases are summarized in Table 2.

The first case (case 1) was a 79-year-old female patient with an amylase of 1.204 U/L (normal range: 28-100 U/L) and lipase value of 16 U/L (normal range: <60 U/L) on day 14 of SARS-CoV-2 PCR positivity. CT was performed on the same day which revealed an edematous pancreas with an increased diameter (Figure 1). Peripancreatic fat plane contamination was observed, and the modified CT severity score was calculated as two. According to the revised Atlanta criteria, two organ failures persisted, and she was considered severe pancreatitis. The Ranson and APACHE 2 scores, which were calculated during pancreatitis diagnosis, were six and 21, respectively. SARS-CoV-2 control PCR test

Table 1. Clinical findings and biochemical results of cases

Case (sex, age)	Amylase (U/L)	Lipase (U/L)	Clinical features		AST/ALT (U/L)	ALP/GGT (U/L)	Total/direct bilirubin (mg/dl)	Calcium (mg/dl)	Triglyceride (mg/dl)	Total cholesterol (mg/dl)	Glucose (mg/dl)
			Fever*	Abdominal pain**							
1 (F, 79)	1204	16	No	Yes	31/64	187/373	1.18/0.53	8.6	283	177	143
2 (M, 64)	395	413	No	Yes	15/33	38/43	0.61/0.13	7.8	-	-	174
3 (F, 74)	1154	1739	Yes	Yes	153/185	87/119	1.02/0.37	8.5	88	148	95
4 (M, 66)	170	375	No	Yes	13/12	71/26	1.21/0.36	8.4	185	207	328

*Fever at the time of amylase/or lipase testing, **Abdominal pain at the time of amylase/or lipase testing.

F: Female, M: Male, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase

Table 2. COVID-19 pneumonia severity scores in lung CT imaging of cases and pancreatitis modified CT severity indices in abdominal CT imaging and Ranson, APACHE, and Atlanta scores of cases and time between pancreatitis and SARS-CoV-2 PCR test positivity detection

Case	COVID-19 pneumonia severity scores	Pancreatitis modified CT severity indices	Ranson scores	APACHE scores	Atlanta scores	Time between pancreatitis and detection of SARS-CoV-2 PCR test positivity (±days)
1	13	2	6	21	Severe	-14
2	0	0	5	11	Mild	-23
3	0	4	2	10	Mild	0
4	0	2	2	8	Mild	-8

COVID-19: Coronavirus diseases-2019, CT: Computed tomography, PCR: Polymerase chain reaction

remained positive. High-resolution CT (HRCT) imaging showed a ground-glass appearance in the bilateral lungs (Figure 2), with a COVID-19 pneumonia severity score of 13. The patient has abdominal pain during her clinical follow-up, but without fever. The patient had no underlying chronic disease, history of alcohol use, previous pancreatitis, or chronic drug use. She had been on favipiravir treatment for 12 days. She survived on day 30 after the SARS-CoV-2 PCR test positivity, but she developed septic shock and died on day 55.

The second case (case 2) was a 64-year-old male patient with diabetes mellitus (DM). His amylase was 395 U/L and lipase was 413 U/L while being followed up in the hospital with COVID-19 diagnosis, on day 23 after PCR positivity for SARS-CoV-2. The pancreas was normal on the same day of HRCT. However, the patient had no contrast-enhanced abdominal CT. Abdominal pain was observed in the clinical follow-up but without fever. SARS-CoV-2 control PCR test remained positive. Survival was observed on day 30 after the first SARS-CoV-2 PCR test positivity. The patient was considered to have mild pancreatitis according to the revised Atlanta criteria, and Ranson and APACHE 2 scores were five and 11 on the day of pancreatitis diagnosis, respectively.

The third case (case 3) is a 74-year-old female patient with hypertension and asthma. She was admitted to the hospital with complaints of epigastric pain and fever. SARS-CoV-2 PCR was positive, amylase and lipase were 1.154 U/L and 1.739 U/L, respectively, in the examinations performed during admission, and CT examination on the same day was compatible with acute pancreatitis. The modified CT score was calculated as four. The

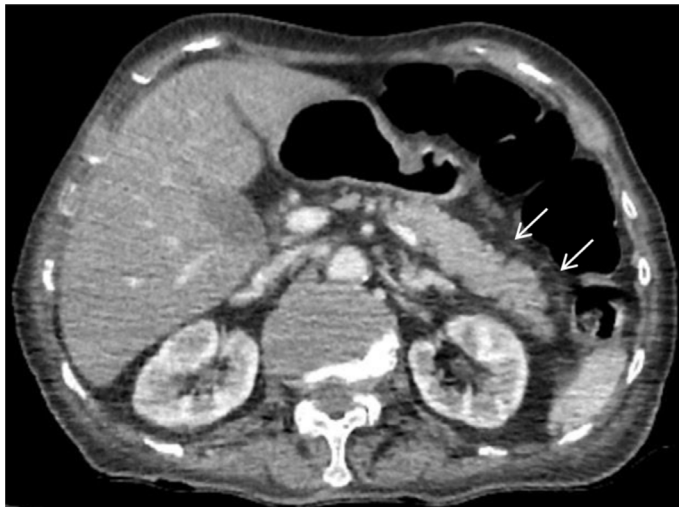

Figure 1. A 79-year-old female patient (case 1) with COVID-19 pneumonia. Contrast-enhanced abdominal CT obtained 13 days later demonstrates mild peripancreatic fat stranding (arrows) consistent with acute pancreatitis

COVID-19: Coronavirus disease-2019, CT: Computed tomography

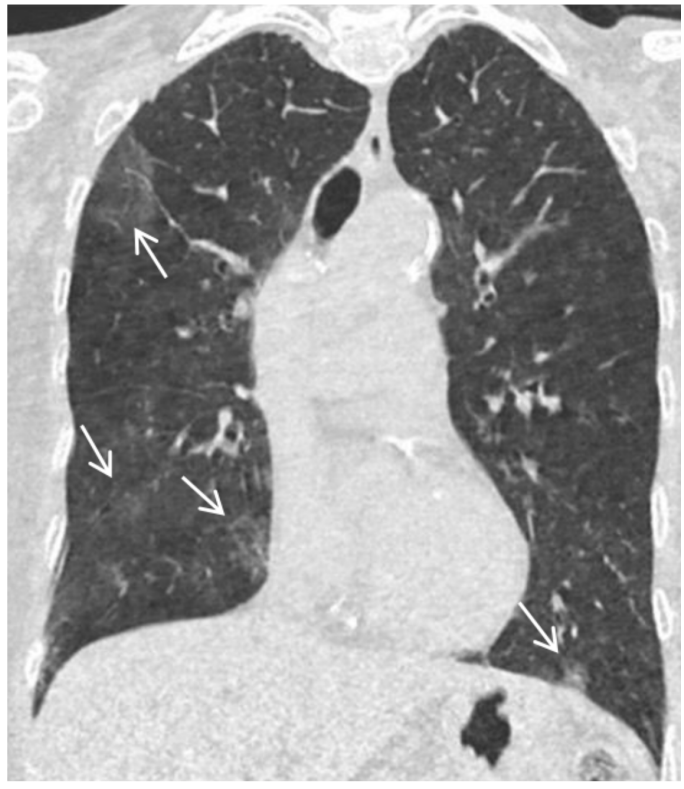

Figure 2. Coronal reformatted chest CT shows ground-glass opacities in bilateral lungs (arrows). The lung CT score was 15 (case 1)

CT: Computed tomography

patient was considered to have mild pancreatitis according to the revised Atlanta criteria, and Ranson and APACHE 2 scores were two and 10 during pancreatitis diagnosis, respectively. There HRCT revealed no COVID-19-compatible involvement. The patient was discharged after being followed up in the ward for four days. Survival was observed on day 30 after SARS-CoV-2 PCR test positivity.

Case 4 is a 66-year-old male patient with a history of hypertension, DM, chronic obstructive pulmonary disease, and acute biliary pancreatitis for two years ago. The patient was admitted to the hospital with the complaint of abdominal pain, but without fever. SARS-CoV-2 PCR was positive. Amylase and lipase were 170 U/L and 375 U/L, respectively, in the examinations upon hospital admission. CT examination on the same day was compatible with acute edematous pancreatitis, with a modified CT severity index of two. The patient was considered to have mild pancreatitis according to the revised Atlanta criteria, and Ranson and APACHE 2 scores during the pancreatitis diagnosis were two and eight, respectively. He was discharged after two days of hospitalization. Survival was observed on day 30 after SARS-CoV-2 PCR test positivity.

None of the cases had a history of azathioprine use. There was no correlation between COVID-19 pneumonia score and pancreatitis severity scores, including Ranson, APACHE 2, and modified CT severity scores. Additionally, no difference was found in terms of COVID-19 pneumonia severity score between the three groups according to the revised Atlanta criteria.

Discussion

The relationship between ACE-2 receptor and SARS-CoV-2 has shown us the importance of the gastrointestinal system in COVID-19 development. The presence of ACE-2 receptor expression in the pancreas, high lipase levels, and clinical pictures in case series/studies, including ours, suggest the severe involvement of the pancreas in this disease course. However, SARS-CoV-2 as a new agent in acute pancreatitis etiology remained unclear. A recent study reported pancreatic injury in 17% of 52 patients admitted with severe COVID-19. However, the pancreatic injury was defined by an increased serum amylase level alone[11]. A further study of 64 patients with severe COVID-19 revealed an 18% with increased in serum amylase concentration, which was attributed to pancreatic injury[2]. Patients who met at least two of the acute pancreatitis criteria were included in our study. The association of elevated amylase alone with pancreatic damage may have caused higher than expected results. Another study from Turkey reported the presence of acute pancreatitis in 12.6% of 316 patients with COVID-19[12]. The acute pancreatitis diagnostic criteria of this prospective study were similar to our study, but our study had lower pancreatitis rates. The retrospective design of the study and the inability to perform abdominal imaging and amylase lipase tests in all patients may explain this difference. A study reported by McNabb-Baltar et al.[13] reported lipase elevation in nine (12.8%) of 71 patients with COVID-19, and lipase was >3 times the upper limit of normal in only two patients, without any acute pancreatitis. Additionally, this study revealed no association between hyperlipasemia and poor outcomes or symptoms, similar to our study[13]. Moreover, a study revealed that increased amylase values were associated with COVID-19. However, this increase may not always be significant in favor of acute pancreatitis alone[14].

Another study that included 985 patients revealed that 17 patients met the acute pancreatitis diagnostic criteria[15], with similar conclusions to our study. An article from Italy stated that pancreatic enzymes were measured in 254 of 282 patients with COVID-19, and severe elevation (>3 times the upper limit of normal) was observed in 11 (4.3%), and two patients met the acute pancreatitis diagnostic criteria[16]. Therefore, the literature revealed different rates, and the rates closest to our study were reported from Italy, with a similar study design[16].

We evaluated a larger population than the studies in the literature. Amylase and/or lipase were tested in 372 of 1.227 patients with positive SARS-CoV-2 PCR who are admitted to our hospital in one year. Our acute pancreatitis rate was 0.3% and 1.07% for all cohorts (n=1.227) and the pancreatic enzyme-tested group (n=372), respectively. Factors, such as the retrospective nature of our study, the inability to measure the amylase and lipase values in every patient, and the genetic differences might have contributed to the relatively low level in our study.

Predicting the course of pancreatitis that develops during and after COVID-19 is difficult. The cytokine storm created by COVID-19 may worsen the course of pancreatitis. However, a study in the literature revealed a better prognosis in COVID-19 cases that presented to the clinic with acute pancreatitis[15]. Besides, the same study revealed that patients who later on developed acute pancreatitis also experienced higher episodes of necrotizing pancreatitis (11.1% vs. 0%), thromboembolic complications (55.6% vs. 12.5%), and higher mortality (37.5% vs. 12.5%)[14].

Pancreatitis severity was not associated with mortality and worsening of clinical course in our study. Furthermore, an increased pancreatitis frequency was not found in patients with severe COVID-19 disease. Our findings of abdominal pain might have been missed because dyspnea is the most prominent symptom in patients with severe COVID-19. Problems experienced in requesting radiological examinations, such as abdominal imaging in patients under intensive care follow-up, and the usual lack of requesting pancreatic-specific

biochemical tests might have contributed to the relatively low pancreatitis rate. Therefore, we recommend that routine follow-up of amylase and lipase values of patients may be appropriate to prevent deficiency at the diagnosis stage, but evaluating the patient holistically, including physical examination and radiological work-up, would be appropriate because enzyme elevation alone may not always be an indicator of clinical damage in terms of acute pancreatitis.

Study Limitations

Limitations of the study include its retrospective nature, amylase/lipase that was not requested from all patients, or tests that could not be performed due to the problems experienced in requesting abdominal CT in patients receiving inpatient oxygen support, and SARS-CoV-2 PCR was not studied in the pancreatic fluid of patients.

Conclusion

In conclusion, our data suggest COVID-19 is a rare risk factor for acute pancreatitis. Symptoms may be missed in patients with severe COVID-19 that are followed up in the intensive care units. Therefore, routine testing of amylase and/or lipase may be suggested for increased diagnosis. There was no correlation between COVID-19 and pancreatitis severity based on our study results. Thus, further data in larger clinical series are needed to confirm our findings.

Ethics

Ethics Committee Approval: The study was approved by the Ministry of Health with the number 2021-02-18T13_06_48 and the Ege University Hospital Ethics Committee with the number E-99166796-0.50.06.04-124496, date: 01.04.2021.

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: D.B.E., N.O., E.G., H.A.E., F.K.A., O.R.S., A.Ö.Ö., C.Ç., T.Y., Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: D.B.E., N.O., E.G., H.A.E., F.K.A., O.R.S., A.Ö.Ö., H.P., M.T., C.Ç., T.Y.

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