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Coronavirus Pandemic

Rare complication spontaneous pneumothorax and pneumomediastinum in COVID-19 patients: A single center experience

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Abstract

Introduction: We aimed to describe the clinical characteristics and outcomes of patients with spontaneous pneumothorax (SPT) and pneumomediastinum (SPM) due to COVID-19 pneumonia.

Methodology: This retrospective study evaluated inpatients at a COVID-19 pandemic hospital. Between March 11, 2020 and March 31, 2021, patients who developed complications of spontaneous pneumothorax (SPT) and pneumomediastinum (SPM) with a confirmed diagnosis of SARS-CoV-2 by polymerase chain reaction (PCR) method were included.

Results: Of the 6,528 hospitalized patients, nine developed complications of SPT and SPM, with an incidence of 0.14%. Four of these patients developed SPT, one developed SPM, one developed SPT + SPM + emphysema, and three developed SPT + SPM. The mean age of the patients was 67.67 ± 13.41 years and the median was 68 (45-88) years. All patients were male. Six patients died, one of whom died of myocardial infarction from uncomplicated causes.

Conclusions: Studies with more cases are needed to evaluate the causality between COVID-19 and pneumothorax (PT) and pneumomediastinum (PM). However, it should be kept in mind that PT and PM may lead to this clinic when sudden respiratory distress occurs in these patients and rapid diagnosis and treatment should be planned. As observed in this study, PT and PM are important factors in the development of mortality in COVID-19 patients.

Key words: COVID-19; spontaneous pneumothorax; pneumomediastinum.

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Introduction

Coronavirus disease 2019 (COVID-19), which emerged in China in December 2019, spread rapidly all over the world and was declared a pandemic by the World Health Organization in March 2020 [1].

The COVID-19 clinic ranges from asymptomatic to critical and fatal disease [2]. Respiratory failure, cardiac and cardiovascular, thromboembolic, neurological, and inflammatory complications are observed due to COVID-19.

PT and PM are rare complications of COVID-19 [3]. These complications can occur at any time during the disease [4]. The etiology of COVID-19-induced PT is unknown. It is thought to be caused by structural changes in the lung parenchyma [3]. In PM, air may be present in the mediastinum with alveolar rupture due to a sudden increase in intrathoracic pressure during Valsalva maneuvers such as coughing and vomiting [5]. PM has been recognized as a complication of COVID-19 in both spontaneously breathing and positive pressure ventilation-dependent patients [6,7].

It has been suggested that the development of SPT and SPM in COVID-19 patients does not increase mortality [8]. However, in another study, it was reported that mortality increased in COVID-19 patients who developed SPT and SPM complications [9].

SPT is the accumulation of air in the pleural space between the lung and the chest wall, in the absence of trauma or iatrogenic causes. SPT is classified as primary and secondary [10]. Primary SPT is defined as primary SPT when it occurs in a healthy individual and secondary SPT when there is a history of underlying lung disease. The diagnosis is based on clinical suspicion and the diagnosis can be confirmed by imaging [11].

In our study, we aimed to describe the clinical characteristics and outcomes of patients with SPT and SPM due to COVID-19 pneumonia. We also wanted to draw attention to the fact that although SPT and SPM are rare complications of COVID-19, they can cause mortality and early detection may change the prognosis.

Methodology

Patients who were hospitalized in the Infectious Diseases pandemic service of Denizli State Hospital between March 11, 2020, and March 31, 2021, were included in the study. SARS-CoV-2 was diagnosed by polymerase chain reaction (PCR) in samples collected from the nasopharynx and oropharynx of the patients. Patients' information was obtained from their epicrisis and hospital records by retrospective review. Demographic information, comorbidities, the day COVID-19 diagnosis on which SPT or SPM complications developed, clinical and laboratory findings [hemogram, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), troponin, D-dimer, ferritin, lactate dehydrogenase (LDH)], treatments, length of hospital or intensive care unit stay and prognosis were recorded. Thoracic computed tomography (CT) scans obtained during the hospitalization of the patients were scored between CO-RADS 0-6 according to the CO-RADS (COVID-19 Reporting and Data System) categorization [12]. The diagnoses of SPT and SPM were confirmed by chest radiography or thoracic CT.

The Ministry of Health guidelines followed in Turkey were based on the dose and duration of glucocorticoids used in the treatment of COVID-19-related hyperinflammatory response. In patients who needed oxygen due to respiratory distress, dexamethasone 6 mg/day or methylprednisolone 0.5-1 mg/kg/day for 10 days or methylprednisolone pulse, ≥ 250 mg (depending on the patient's risk factors and clinical condition) was used according to the guideline recommendation [13].

Inclusion criteria

Patients over 18 years of age with a diagnosis of COVID-19 and the presence of PT or PM admitted between March 11, 2020, and March 31, 2021, were included in the study.

Exclusion criteria

Iatrogenic PT and PM cases secondary to positive pressure ventilation were excluded. Among the 4086 patients hospitalized with a diagnosis of COVID-19 in the hospital during the same period, PCR-negative cases and cases that could not be confirmed by repeated PCR were excluded.

The study was approved by the Non-Interventional Ethics Committee of Pamukkale University Faculty of Medicine with the decision dated 03/12/2021 and numbered E137032.

Statistical analysis

Statistical analysis of the data was performed with the Statistical Package for Social Sciences (SPSS) 25 (Inc. Chicago, Illinois, USA), and continuous variables were expressed as mean ± standard deviation, minimum and maximum values, and categorical variables as number and percentage.

Results

Between March 11, 2020, and March 31, 2021, 6,528 patients with a confirmed diagnosis of COVID-19 by RT-PCR received inpatient hospital treatment. Of these patients, four out of nine developed SPT, one developed SPM, one developed SPT + SPM + subcutaneous emphysema, and three developed SPT + SPPM (Table 1). The mean age was 67.67 ± 13.41 years

Table 1. Demographic and clinical characteristics of patients with spontaneous pneumothorax and pneumomediastinum due to COVID-19 pneumonia.

Patient	Age	Comorbidity	SPT/SPM	Antibiotics	Methylprednisolone CS	Smoking history	Is he alive?
Patient 1	78	DM COPD	SPM	PTZ, LEV	2 × 40mg/day, 10 days	No	Yes
Patient 2	45	None	SPT	PTZ, LEV	2 × 40mg/day, 10 days	Yes	Exitus
Patient 3	58	None	SPT, SPM	PTZ, LEV	250 mg, 5 days	Yes	Yes
Patient 4	76	HT	SPT, SPM, subcutaneous emphysema	MEM, LEV	6 mg/day, dexamethasone, 10 days	No	Exitus
Patient 5	75	DM, Subdural hematoma	SPT	PTZ, LEV	2 × 40 mg/day, 10 days	No	Exitus
Patient 6	67	BPH	SPT, SPM	PTZ, LEV	2 × 40 mg/day, 14 days	No	Exitus
Patient 7	68	HT	SPT, SPM	CRO	2 × 40 mg/day, 10 days	Yes	Exitus
Patient 8	88	CRF,Colon cancer	SPT	CRO	-	No	Yes
Patient 9	54	Colon cancer, CAD	SPT	PTZ, LEV	6 mg/day, dexamethasone, 4 days	Yes	Exitus

DM: Diabetes mellitus; COPD: chronic obstructive pulmonary disease; HT: Hypertension; BPH: Benign prostatic hypertrophy; CRF: chronic renal failure; CAD:Coronary artery disease SPT: Spontaneous Pneumothorax; SPM: Spontaneous Pneumomediastinum; CS: Corticosteroid; PTZ: Piperacillin-tazobactam; LEV: Levofloxacin; MEM: Meropenem; CRO: Ceftriaxone.

and the median was 68 (45-88) years (Table 2). All patients were male.

The total length of hospital stay ranged from a minimum of four and a maximum of 25 days, with a mean of 17.89 ± 6.53 days and a median of 19 days. The mean duration of hospitalization until complications developed was 9 ± 5.77 days and the median was 10 (3-17) days (Table 2).

Medical history revealed that four patients were smokers. Regarding comorbidities, two patients had no known history of chronic diseases. One patient had hypertension (HT), one patient had benign prostatic hypertrophy (BPH), one patient had diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD), one patient had DM and subdural hematoma, one patient had colon cancer and coronary artery disease, and one patient had colon cancer and chronic renal failure (CRF).

All patients underwent thoracic CT at their first hospital admission. When pulmonary involvement was assessed on thorax CT, patients aged 78, 76 and 67 years had CO-RADS 5; patients aged 45 and 58 years had CO-RADS 4; patients aged 75, 68, 88, and 54 years had findings consistent with CO-RADS 3. Nine patients had complaints of dyspnea at the time of first admission to the emergency department, all except the 88-year-old patient were hypoxic and had a saturation of less than 90. The 88-year-old patient had dyspnea, a saturation of 92% in arterial blood gas (ABG), and moderate pneumonia with bilateral ground glass areas on the thorax CT. The remaining eight patients had bilateral diffuse ground glass areas and severe pneumonia on thorax CT.

ABG was obtained and posteroanterior chest radiography or thoracic computed tomography (CT) was performed in patients with increased shortness of breath, chest pain, and increased oxygen demand. Complications were detected in these imaging studies (Figure 1). Four of the nine patients continued treatment without thoracic tube placement. Of these patients without a tube, the 76-year-old patient was excised, while the other patients recovered and were discharged. One patient was given an oxygen condenser at

Figure 1. Chest radiographs and thorax computed tomography images of patients with spontaneous pneumothorax and pneumomediastinum due to COVID-19 pneumonia. Patient 1: Spontaneous pneumomediastinum image in thoracic computed tomography. Patient 2: Spontaneous pneumothorax image in chest radiographs

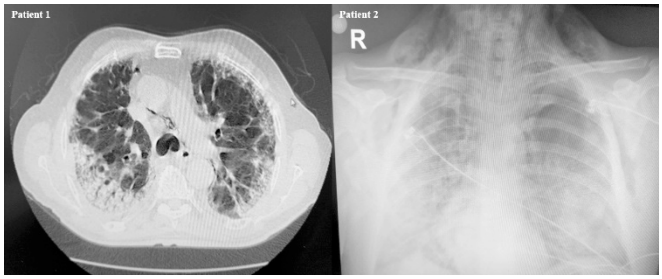


Table 2. Demographic and clinical characteristics and laboratory values of patients with spontaneous pneumothorax and pneumomediastinum due to COVID-19 pneumonia.

		Mean ± SD	Med (min - max)
Age		67.67 ± 13.41	68 (45 - 88)
Gender (n; %)	Male	9 (100%)	
Prognosis (n; %)	Ex	6 (66.7%)	
	Alive	3 (33.3%)	
Anticoagulant (n; %)	Yes	8 (88.9%)	
Smoking (n; %)	Exist	4 (44.4%)	
	None	5 (55.6%)	
Thoracic tube (n; %)	Yes	5 (55.6%)	
	No	4 (44.4%)	
Intubation (n; %)	Yes	3 (33.3%)	
	No	6 (66.7%)	
Exitus (n; %)	Complication ex	5 (55.6%)	
	Non complication ex	1 (11.1%)	
	Alive	3 (33.3%)	
How many days did he serve		17.89 ± 6.53	19 (4 - 25)
Complication on what day of hospitalization		9 ± 5.77	10 (3 - 17)
WBC (K/µL)		11821.11 ± 4619.62	11400 (4200 - 20900)
PNL (K/µL)		10568.89 ± 4445.06	9560 (3700 - 20100)
Lenfosit (K/µL)		741.11 ± 450.6	690 (170 - 1570)
Platelet (K/µL)		206444.44 ± 80392.96	198000 (86000 - 358000)
CRP (mg/L)		102.56 ± 96.47	63 (8 - 241)
Sedimentation (mm/h)		47.44 ± 25.81	50 (6 - 80)
Troponin (ng/L)		830.8 ± 1785.26	15.1 (5.2 - 5300)
D-Dimer (ng/mL)		6.69 ± 9.14	3.1 (0.8 - 30)
Ferritin (ug/L)		872.78 ± 727.63	600 (241 - 2600)
LDH (U/L)		523.56 ± 316.58	424 (221 - 1246)

discharge and after using it for three months, he did not use it because he had good saturations in room air. The other three patients were contacted by telephone for information and did not return to the hospital with similar complaints. During follow-up, intubation was indicated in three patients. These patients died in intensive care. In addition to favipiravir and methylprednisolone, the preferred antibiotics for possible bacterial infections in patients with elevated CRP and sedimentation were ceftriaxone, levofloxacin, piperacillin-tazobactam and meropenem. One patient received methylprednisolone at a dose of 250 mg for five days. One patient did not require steroid treatment. While 2 × 40 mg methylprednisolone was given for 10 days in five patients, it was given in the same dose for 14 days in one patient due to continuing respiratory distress. One patient was also able to receive 6 mg/kg/day of dexamethasone treatment for four days since he died on the fourth day of hospitalization. The steroid treatments administered to patients are presented in Table 1. Enoxaparin treatment was administered to all patients except the patient with subdural hematoma.

The results of hemogram, ESR, CRP, troponin, D-dimer, ferritin, and LDH tests are summarized in Table 3.

SPM complication developed in a 78-year-old patient with underlying diagnoses of DM and COPD. The patient who was extubated and followed up without a thoracic tube was discharged after recovery. A 45-year-old patient with SPT without known comorbidities was followed up in the ward with right and left thoracic tube placement. During follow-up, respiratory distress increased and the patient was intubated, resulting in excitus. A 58-year-old patient with no known comorbidities developed SPT + SPM complications. The patient was followed up and treated extubated without thoracic tube insertion and recovered. A 76-year-old extubated patient with hypertension developed complications of SPT + SPM + subcutaneous emphysema. A left thoracic tube was inserted and the patient died on the 17th day of follow-up. SPT developed in a 75-year-old COVID-19-positive patient with a diagnosis of DM and subdural hematoma. He was treated with a left thoracic tube. The patient was intubated upon increasing respiratory distress and died. Complications of SPT + SPM developed in a 67-year-old patient with no comorbidities other than benign prostatic hypertrophy and a left thoracic tube was inserted. While the patient was followed extubated, he was intubated due to low saturation and was lost. SPT complication developed in an 88-year-old patient with colon cancer and CRF. The patient was followed up extubated without thoracic tube insertion and died on the 20th day. A 54-year-old patient with comorbidities of coronary artery disease and colon cancer underwent right thoracic tube insertion due to SPT complications. The patient was extubated and died. A 68-year-old patient with SPT + SPM and underlying hypertension died of myocardial infarction, so mortality was not directly related to these complications. This patient was followed and extubated in the ward.

Discussion

The incidence of SPT in COVID-19 patients is currently unknown. The first reports in the literature were mostly case reports [2-5]. However, in one study, 902 nasopharyngeal swabs of 3368 patients evaluated with suspicion of COVID-19 pneumonia were found to be positive and SPT developed in six of them and the incidence was calculated as 0.66% [3]. In Spain, in a case-control study conducted in patients with and without SPT in COVID-19 patients admitted to the emergency department, the frequency of SPT was 0.56% and it was calculated that COVID-19 increased the risk of developing SPT 4.1-fold [14]. In our study, SPT and SPM were detected in 9 patients among the patients who were followed up with the diagnosis of COVID-19 disease and the incidence was 0.14%.

Table 3. Laboratory results of patients with spontaneous pneumothorax and pneumomediastinum due to COVID-19 pneumonia.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
WBC (K/µL)	11.400	12.000	9730	20.900	14.500	14.570	9940	4200	10.200
PNL (K/µL)	8730	11.100	8050	20.100	11.680	13.000	9200	3700	9560
Lenfosit (K/µL)	1570	480	410	790	1270	900	390	250	170
Platelet (K/µL)	358.000	238.000	116.000	86.000	181.000	268.000	198.000	190.000	223.000
CRP (mg/L)	8	135	229	75	187	63	10	28	241
Sedimentation (mm/h)	29	69	68	80	70	50	6	25	30
Troponin (ng/L)	9.8	9.1	15.1	1890	5.2	215	20	13	5300
D-Dimer (ng/mL)	4.4	1	0.8	30	3.1	8	8	2.9	2
Ferritin (ug/L)	516	2600	710	362	479	1055	1292	241	600
LDH (U/L)	369	550	424	660	221	1246	665	240	337

WBC: White blood cell; PNL: Polymorphonuclear leukocyte; CRP: C-reactive protein; LDH: Lactate dehydrogenase.

In a multicenter study, 60 patients with PT and 11 with PM were evaluated in a heterogeneous group of patients followed up for coronavirus infection. It was observed that 46 of those with PT and all of those with PM were in the male gender, survival was lower in those aged 70 years and older compared with younger people, and no difference was found between genders in twenty-eight-day survival [8]. Male gender has been reported as a risk factor for PT not related to COVID-19 [11]. Similar to the literature, male gender was found to be a risk factor in our study. Rafiee *et al.* reported that five patients with COVID-19 pneumonia developed SPT and one developed SPM and male gender was one of the risk factors for these complications [4]. In our study, there was no female gender in nine patients who developed SPT and SPM.

The mean age of our patients was 67.6 ± 13.4 years. In the study of six patients with SPT and SPM not dependent on mechanical ventilation, the patients were found to be male, three patients had COPD and the patients were over 29 years of age. It has been reported that alveolar damage in the fibrotic stage and ruptured small cysts may lead to PT and PM with increased intrathoracic pressure during severe coughing in these patients [4]. In another study, it was reported that four of the patients who developed PT due to COVID-19 pneumonia were female and two were male, with a minimum age of 47 years and a maximum age of 81 years [3]. In the study by Shaikh *et al.* DM was found to be the most common comorbidity and the mean age was 51.5 ± 13.3 years [9]. It was thought that the differences in age limits could be attributed to different underlying diseases.

Figure 3. Chest radiographs and thorax computed tomography images of patients with spontaneous pneumothorax and pneumomediastinum due to COVID-19 pneumonia. Patient 5: Spontaneous pneumothorax image in chest radiographs. Patient 6: Spontaneous pneumothorax and spontaneous pneumomediastinum images in chest radiographs. Patient 7: Spontaneous pneumothorax and spontaneous pneumomediastinum images in chest radiographs and thorax computed tomography

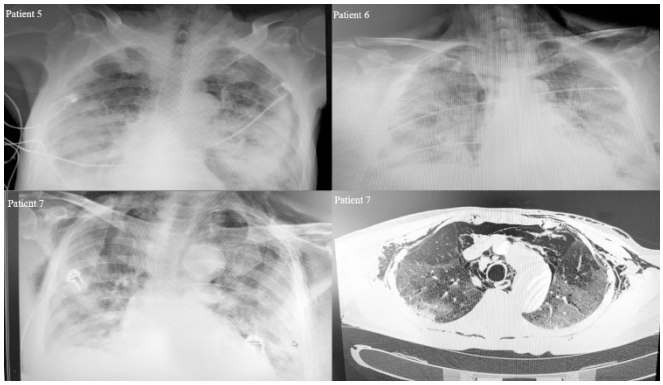
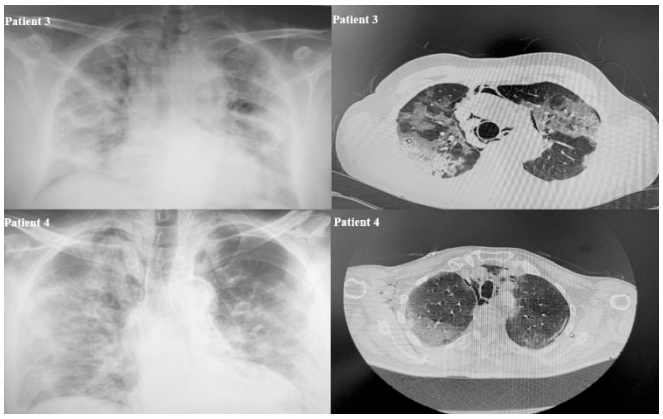


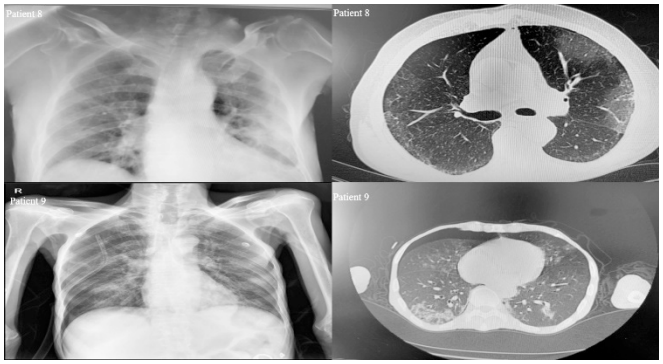
Figure 2. Chest radiographs and thorax computed tomography images of patients with spontaneous pneumothorax and pneumomediastinum due to COVID-19 pneumonia. Patient 3: Spontaneous pneumothorax and spontaneous pneumomediastinum images in chest radiographs and thorax computed tomography Patient 4: Spontaneous pneumothorax, spontaneous pneumomediastinum and emphysema images in chest radiographs and thorax computed tomography



SPT is diagnosed with history, imaging, and physical examination findings. PT is recognized by the separation of the visceral pleural line with a line on chest radiography [10]. In addition, Thoracic CT has an important role in the rapid diagnosis of pulmonary complications associated with COVID-19 [15]. In this study, imaging modalities were performed based on the clinical suspicion of the patients. Six patients were diagnosed by thorax CT and three by chest radiographs (Figure 1,2,3,4).

In COVID-19, pulmonary epithelial and endothelial damage, alveolar-capillary barrier dysfunction, impaired lung tissue repair, decreased fibrinolysis, and diffuse vascular thrombosis findings are pathological

Figure 4. Chest radiographs and thorax computed tomography images of patients with spontaneous pneumothorax and pneumomediastinum due to COVID-19 pneumonia. Patient 8 and 9: Spontaneous pneumothorax images in chest radiographs and thorax computed tomography



findings as a result of cytopathic, inflammatory, and immune responses [16]. It has been emphasized that inflammation of the pulmonary parenchyma, consolidation, necrosis, formation of cystic and cavitary lesions in the lungs, and the presence of a fistula between the parenchyma and the pleura may be one of the causes that trigger CPT, but it is not sufficient for causality in a single mechanism [17]. In the study of Shan *et al.*, it was stated that the prognosis of SPT in COVID-19 pneumonia may be related to the severity of the lung lesion, but no clear correlation was reported for this relationship [18]. When the patients in our study were evaluated, one patient had a moderate course and eight patients had severe pneumonia according to the imaging performed at the time of initial hospital admission. Damage due to initial basal pulmonary inflammation involvement may be a risk for SPT and SPM complications. However, we think that a case-control study should be performed to reach this conclusion.

In another study, when 1100 patients with COVID-19 pneumonia were evaluated, it was reported that 43 patients had SPT, SPT + SPM complications, and the most common comorbidity of these patients was diabetes mellitus (30.2%). When other underlying diseases were analyzed, hypertension was found in 23.3% and chronic renal failure in 11.6%, but these comorbidities were found to have no effect on the development of SPT and SPM [9]. In a study, three male patients over 60 years of age who developed PT and PM complications had comorbidities of hypertension, multiple myeloma, pulmonary emphysema, hypercholesterolemia, and previous ischemic stroke [19]. In this study, chronic renal failure (CRF), colon cancer, DM, subdural hematoma comorbidities were detected. In the study by Hallifax *et al.* chronic lung disease was reported as a risk factor for CP [20]. However, in contrast to this study, one patient had COPD and the other patients did not have a history of respiratory diseases.

Smoking has been reported as a risk factor for SPT [21]. A study evaluating SPT cases in the emergency department, it was reported that 71.7% of the patients had a history of smoking but this was not statistically significant [11]. In a case-control study evaluating risk factors for SPT due to COVID-19, it was found that there was no association with smoking [14]. In our study, two of the four patients who were smokers died, and the other three patients who died had no history of smoking. Due to the small number of cases, the causal relationship between smoking and mortality was not specified.

Methylprednisolone, which has an anti-inflammatory effect, is used in critically ill COVID-19 patients. In a study evaluating methylprednisolone pulse therapy, 156 patients received corticosteroid treatment, 17 of whom received pulse methylprednisolone (≥ 250 mg/day for 3 days), followed by a dose of 0.5-1.0 mg/kg/day every three to seven days. Seven patients were reported to have died and ten to have recovered. As a result, pulse methylprednisolone treatment was found to be effective in patients under 70 years of age [22]. In the study by Zantah *et al.,* it was reported that corticosteroids were administered in five of six patients [3]. In our study, six patients received 2 × 40 mg/day methylprednisolone, and two patients received 6 mg/day dexamethasone during COVID-19 treatment. Only one patient was treated with 250 mg/day methylprednisolone for five days. One patient did not receive any glucocorticoid treatment. These three patients who did not receive corticosteroid treatment, who received pulse steroids, and who received lower doses, respectively, survived. Mortality was observed in six patients who received other glucocorticoids. Studies involving a larger number of patients are needed to evaluate the type, dose, duration, and efficacy of the corticosteroids we use in patients who require oxygen.

It has been reported that the onset time of COVID-19-related PT, and hospitalization of patients was on average 9-19.6 days and invasive mechanical ventilation was 5.4 days later [23]. In seven patients, radiological evidence of spontaneous air leakage was found with a mean of 9 ± 9 days after the onset of COVID-19 symptoms and a mean of 6 ± 8 days after hospitalization [24]. Similar to our study, the mean time to complication development was 9 ± 5.77 days after admission.

Lymphopenia and elevated CRP, LDH, ferritin, and D-dimer were detected in most patients. Lymphopenia, ferritin, CRP, LDH, and D-dimer elevation are known to be poor prognostic factors [25]. These biomarkers may lead to multi-organ damage or ARDS resulting in a cytokine storm. In severe COVID-19 cases, the hyper-inflammatory process may result in alveolar damage and rupture [26]. The complications in our patients may be attributed to this mechanism. Various biomarkers were assessed to determine the severity of the disease in 10.491 confirmed COVID-19 patients from 32 studies in different geographical regions. In this meta-analysis study, it was found that decreased lymphocyte and platelet counts, increased CRP, creatinine kinase, procalcitonin, LDH, D-dimer, alanine aminotransferase, aspartate aminotransferase, and

creatinine levels were significantly associated with poor outcomes [27]. It was reported that microangiopathy and thrombosis were observed in the lungs of patients who developed ARDS due to COVID-19 infection [28]. Because of the risk of thrombosis, all patients received prophylactic or therapeutic doses of anticoagulant therapy unless contraindicated. Except the patient who developed a myocardial infarction, no additional cardiovascular pathologies occurred in the other patients.

The limitations of the study are that it was a retrospective, single-center study conducted in a certain period. PCR negativity does not exclude the diagnosis of COVID-19, but only PCR-confirmed cases are presented here. A multi-center study including PCR-negative patients diagnosed with COVID-19 would have enabled a more comprehensive evaluation.

Conclusions

Studies with more cases are needed to evaluate the causality between COVID-19 and PT and PM. However, it should be kept in mind that PT and PM may lead to this clinic when sudden respiratory distress occurs in these patients and rapid diagnosis and treatment should be planned. Especially PT can be an important cause of morbidity and mortality in COVID-19.

We think that the data in this study, in which cases without iatrogenic causes are presented, will contribute to the literature.

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