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Original Research

Clinical, Laboratory and Radiological Evaluation of Intensive Care Patients Who Developed COVID-19 Associated Pneumomediastinum

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ABSTRACT

Objective: This study aims to identify possible risk factors and clinical, laboratory, or radiological predictors for COVID-19 associated pneumomediastinum.

Methods: Patients who developed pneumomediastinum under mechanical ventilation (MV) due to COVID-19 pneumonia during intensive care unit (ICU) (Group 1), and patients who died without developing pneumomediastinum during ICU (Group 2) were compared statistically in terms of age, laboratory parameters, medical treatments, mechanical ventilator parameters, and radiological findings.

Results: Group 1 patients were significantly younger than Group 2 patients ($p<0.05$). There was no significant difference between groups in terms of laboratory parameters except N/L ratios and sedimentation rates ($p>0.05$). There was no significant difference between the groups in terms of dominant infiltration pattern, pleural and pericardial effusion ($p>0.05$). The incidence of organizing pneumonia pattern, and infiltration of more than 75% of the total lung parenchyma were significantly higher in Group 1 ($p<0.01$). The rates of favipiravir treatment, immunomodulatory therapy and prone positioning were significantly lower in Group 1 than Group 2 ($p<0.01$). There was no significant difference between groups in terms of the duration of ICU hospitalization and MV, $PEEP_{max}$, PIP_{max} and PaO_2/FiO_2 ($p>0.05$).

Conclusion: Care should be taken in terms of pneumomediastinum in patients who show diffuse organized pneumonia patterns affecting more than 75% of the parenchyma area.

Keywords: COVID-19, pneumomediastinum, mortality, Computed Tomography

INTRODUCTION

It is known that SARS-CoV-2 virus, which has high infectivity rates, is asymptomatic or shows mild upper respiratory tract infection findings in most of the young and immunocompetent cases [1]. The virus infiltrating the lower respiratory tract, alarming the immune system and creating a cytokine storm may result in severe pneumonia [2]. Pulmonary involvement, which resolves within a few weeks without sequelae during the natural course of the disease in most of the cases, leads to more serious respiratory distress in immunosuppressive patients

and in the presence of comorbid disorders such as diabetes and hypertension [3,4]. In these patients, respiratory support may be required and even mechanical ventilator may be needed in the intensive care unit (ICU). It was noted that spontaneous pneumomediastinum (PM) developed in some cases in the course of COVID-19-related pneumonia, in some cases PM developed due to mechanical ventilation during intensive care treatment, and most of the patients who developed PM died in a short time [5,6]. Thereupon, a number of publications have been reported about PM, one of the most mortal complications of COVID-19 pneumonia; however, this situation has not yet been systematically evaluated [5,6]. In this study, we evaluated the patients who received respiratory support with a mechanical ventilator in the ICU and developed PM during the treatment together with their clinical, laboratory, medical and radiological features as a whole and compared with patients who did not developed PM during ICU. In this way, we aimed to give an idea to clinicians in terms of taking the necessary precautions in high-risk cases by determining possible risk factors or predictive parameters for PM.

MATERIALS AND METHODS

Study Population

SARS-CoV-2 PCR positive patients who were treated in the ICU of our hospital due to COVID-19 pneumonia between March 2020 and March 2021 and had a thorax computed tomography (CT) exam at the time of first admission to the hospital were included in the study to evaluate the radiological effect on PM objectively. The patients were divided into 2 groups; Group 1:Patients in ICU who developed PM at any stage of the disease, and Group 2:Patients who were treated in the ICU due to COVID-19 pneumonia and died, but never developed PM during the disease. The diagnosis of PM was made with the presence of subcutaneous emphysema in physical examination, X-Ray, and/or CT findings.

Main Points;

- Advanced age, male gender, and comorbid disease are not risk factors for the development of pneumomediastinum.
- The probability of pneumomediastinum is high in cases where the organizing pneumonia pattern diffusely affects more than 75% of the lung parenchyma area.
- Immunomodulatory and antiviral therapies may be preventive for the development of pneumomediastinum.
- Treating intensive care patients in prone position may prevent the development of pneumomediastinum.
- There is no direct relationship between increased intraalveolar pressure as a result of invasive mechanical ventilation and pneumomediastinum.

All Group 1 cases consisted of patients who developed PM while under invasive/noninvasive mechanical ventilator therapy. Spontaneous PM cases that developed during outpatient or inpatient treatment were excluded for Group 1 in order to evaluate the effect of mechanical ventilator on PM. Age, comorbid diseases, and mean durations of ICU hospitalization, durations of treatment with mechanical ventilator were recorded for both of groups. Also for Group 1, on which day of the mechanical ventilation PM developed was calculated (MV-PM interval).

Ethics committee approval was obtained for the study from the Acibadem University Clinical Research Ethics Committee (Date: 2021-03-10, Approbval Number: 2021-05/03).

Laboratory Parameters

Daily laboratory tests were performed on all patients for both groups. Laboratory parameters were taken into account before the development of PM in Group 1 patients and during all ICU hospitalizations in Group 2 patients. Laboratory parameters, including parameters predictive of severe disease or complications, hemoglobin (highest/lowest; Hb_{max}, Hb_{min}), platelet (highest/lowest, PLT_{max}, PLT_{min}), highest neutrophil (N_{max}), and the levels of leukocyte (Leu_{max}), lowest lymphocyte (L_{min}), highest neutrophil/lymphocyte ratio (N/L_{max}), $D\text{-}Dimer_{max}$, LDH_{max}, $Procalcitonin_{max}$, $Ferritin_{max}$, $Fibrinogen_{max}$, $IL\text{-}6_{max}$, CRP_{max} accounts and erythrocyte sedimentation rate (ESR_{max}) were evaluated. In addition, secondary viral, bacterial and/or fungal infection during the ICU of the patients and isolated agents were recorded.

Radiological Evaluation-CT Imaging Method and Image Analysis

All cases had tomographic exams since the patients who had at least one thorax CT exam at the time of first admission before they were taken to the ICU were included in the study. Patients with CT images were selected for the study in order to make an optimal assessment of the predictivity of radiological parameters on PM. Since ground-glass opacities (GGOs), crazy-paving patterns, low level of pleural-pericardial effusion are not usually seen on X-Ray.In patients with multiple CT scans, the most progressive CT imaging features obtained at the time of

development of PM for Group 1 and the most progressive of all CTs in Group 2 were evaluated. Radiologic evaluations after admission to the ICU were made with portable radiographies. However, radiography features were not evaluated in the study. All CT scans were done with Siemens Somatom Sensation-Syngo CT 2009 device using a low-dose noncontrast CT protocol. The acquisition parameters were standardized as: tube voltage, 140 kV; tube current, 40 mA; pitch, 1.4; FOV, 455 mm; slice thickness, 64×0.6 mm. Images were converted into 1 mm thin reconstructions in the lung parenchyma window.

All images were evaluated separately by two radiologists with approximately 25 years (D.Y.) and 10 years (D.E.T.S) of practical experience in chest CT. Radiologically typical/atypical presentations of cases were evaluated according to the criteria of the Radiological Society of North America (RSNA) Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19, as of April 2020 [7].

CT imaging features were evaluated according to the RSNA guideline, as are typical/atypical imaging features for COVID-19 pneumonia, the presence of organized pneumonia, presence of unilateral/bilateral involvement, dominant infiltration pattern (ground-glass opacities, crazy-paving, consolidation), the distribution of GGOs, crazy-paving, and consolidation patterns were classified as peripheral (distal 1/3 of lung parenchyma), central and diffuse, while lobar distribution pattern of infiltrates (lower lobes-upper lobes-widespread) [7,8]. The percentage of infiltrating total lung parenchyma (1, <25%; 2, 25%–50%; 3, 50%–75%; 4, >75%) were also calculated in multiplanar images [7,9]. The affected lung areas were measured electronically in continuous reconstructed axial sections 10 mm section thickness, then the sum of the sequential areas was recorded. These measurements were all achieved by MPR images with Syngo.Via Software (VB10B, Siemens). In atypical or suspicious cases, CT images were reevaluated together and a consensus was reached.

Although the diagnosis of PM was made clinically in patients who developed PM, it was also proven radiologically. In other words, CT images were taken even after PM developed in Group 1 patients.

Medical Treatment and Mechanical Ventilator Pressures

Patients were evaluated according to which SARS-CoV-2 targeted drugs they took during their treatment (hydroxychloroquine, azithromycin, favipiravir) and whether they received immunomodulatory treatment (glucocorticoid, anti-cytokine drugs). The mechanical ventilator (MV) pressure parameters ($PEEP_{max}$, PIP_{max}) ve PaO2/FiO2 were recorded. In addition, the prone position application status of the patients was evaluated.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. Student-t test was used for comparisons between two groups of normally distributed quantitative variables, and Mann-Whitney U test was used for comparisons between two groups of non-normally distributed quantitative variables. Pearson chi-square test, Fisher's exact test and Fisher-Freeman-Halton test were used to compare qualitative data. Statistical significance was accepted as $p<0.05$.

RESULTS

A total of 38 patients were included in the study; 16 patients in Group 1, and 22 in Group 2. The mean age of the patients was 61,79±15,49 (16-95) and it was significantly lower in Group 1 (Group 1 mean age: 53.94±14.87; Group 2 mean age 67.50±13.55) (p=0.006) (Table 1). Although the number of male patients was higher than females in both groups, There was no significant difference between the groups in terms of gender and presence of additional disease (p=0.310, p=0.290, respectively) (Table 1). PM developed while all Group 1 patients were under mechanical ventilator therapy in the ICU.

The mean interval between the first admission to the ICU and the development of PM of Group 1 patients was 19.81±9.42 (9-35) days. The mean interval from MV to developing PM was 13.68±10.73 (1-30) days in Group 1 patients. The mean duration of ICU hospitalization of Group 1 patients was 29.1±9.6 (12-46) days, while that of Group 2 patients was 37.8±30.7 (1-150). While the mean duration of MV in Group 1 patients was 23±11.4 (5-40) days, it was 35.4±29 (1-140) days in Group 2 patients. There was no statistically significant difference between the groups in terms of the duration of ICU hospitalization and mechanical ventilation (p=0.293; p=0.124, respectively) (Table 1). Only 3 of Group 1 patients was discharged; 13 patients died (mortality rate 81.25%).

Table 1. Clinical and Laboratory Results by Presence of Pneumomediastinum

Total (n=38)		Pneumomediastinum			
		Yes (n=16)	No (n=22)	p	
Age	*Min-Max (Median)*	16-95 (59.5)	16-74 (57.5)	41-95 (69.5)	[a]***0.006***
	Mean±SD	61.79±15.49	53.94±14.87	67.50±13.55	
Gender	*Female*	28 (74)	12 (75)	16 (73)	[b]***0.310***
	Male	10 (26)	4 (25)	6 (27)	
Comorbidity	*No*	13 (34.2)	7 (43.8)	6 (27.3)	[b]***0.290***
	Yes	25 (65.8)	9 (56.3)	16 (72.7)	
Hospitalization in the ICU (day)	*Min-Max (Median)*	1-150 (28)	12-46 (27.5)	1-150 (30)	[a]*0.293*
	Mean±SD	34.2±24.5	29.1±9.6	37.8±30.7	
Mechanical ventilation (day)	*Min-Max (Median)*	1-140 (22)	5-40 (21)	1-140 (27.5)	[a]*0.124*
	Mean±SD	30.2±24	23±11.4	35.4±29	
Hemoglobin *(g/dL)*	*Min-Max (Median)*	8.6-13.5 (11.1)	9.2-12.7 (11.2)	8.6-13.5 (11.1)	[a]***0.798***
	Mean±SD	11.15±1.23	11.09±1.23	11.19±1.26	
Leukocyte *(uL)*	*Min-Max (Median)*	3400-72250 (19425)	3400-31700 (17635)	9000-72250 (19480)	[c]***0.231***
	Mean±SD	21545.53±11709.25	18270±7716.37	23927.73±13598.48	
Neutrophil *(uL)*	*Min-Max (Median)*	1300-55600 (17700)	1300-27700 (17300)	7670-55600 (17700)	[a]***0.186***
	Mean±SD	18400±9898.83	15886.88±7981.67	20227.73±10900.77	
Lymphocyte *(uL)*	*Min-Max (Median)*	150-3000 (465)	150-3000 (615)	150-840 (425)	[c]***0.308***
	Mean±SD	592.37±520	773.13±745.45	460.91±191.04	
N/L	*Min-Max (Median)*	1.4-161.3 (28.1)	4-161.3 (19.5)	1.4-152.7 (39.8)	[c]***0.017****
	Mean±SD	44.76±42.23	33.00±41.44	53.31±41.64	
Platelets *(×10³ /uL)*	*Min-Max (Median)*	90-447.5 (252.3)	90-391.5 (244.3)	116.5-447.5 (263)	[a]***0.242***
	Mean±SD	255.24±89.61	235.06±82.32	269.91±93.66	
IL-6 *(pg/mL)*	*Min-Max (Median)*	2-290 (54)	5.6-177 (48.9)	2-290 (68.4)	[c]***0.301***
	Mean±SD	75.11±76.34	51.32±39.23	92.42±91.78	
CRP*(mg/dL)*	*Min-Max (Median)*	1.2-59.3 (24.9)	1.2-58.7 (21.6)	9.1-59.3 (26.4)	[a]***0.214***
	Mean±SD	23.99±13.27	20.82±14.8	26.3±11.86	
ESR *(mm/h)*	*Min-Max (Median)*	4-150 (58.5)	56-150 (92.5)	4-67 (31)	[a]***0.001****
	Mean±SD	59.55±34.86	91.88±25.06	36.05±17.84	
D-dimer *(µg/mL)*	*Min-Max (Median)*	0.5-15.4 (4)	1.5-12 (5)	0.5-15.4 (2.6)	[c]***0.174***
	Mean±SD	4.75±3.72	5.45±3.27	4.24±4.01	
LDH *(IU/L)*	*Min-Max (Median)*	50-1638 (397)	185-1638 (382)	50-1076 (416.5)	[c]***0.679***
	Mean±SD	481.11±290.68	481.19±332.61	481.05±264.29	
Ferritin *(ng/mL)*	*Min-Max (Median)*	123-16500 (1518.5)	129-16500 (1582.5)	123-8853 (1482)	[c]***0.615***
	Mean±SD	1958.24±2914.39	2499.38±3980.24	1564.68±1806.58	
Fibrinogen *(mg/dL)*	*Min-Max (Median)*	118-900 (485)	411-900 (631)	118-804 (305)	[a]***0.001****
	Mean±SD	495.34±222.38	627.25±161.2	399.41±213.71	

Procalcitonin *(ng/mL)*	*Min-Max (Median)*	0.01-108 (2.42)	0.1-75.5 (1.55)	0.01-108 (3.4)	***[c]0.139***
	Mean±SD	9.80±21.32	7.02±18.53	11.82±23.34	
Secondary Infection	*No*	17 (44.7)	12 (75.0)	5 (22.7)	***[b]0.001*****
	Yes	21 (55.3)	4 (25.0)	17 (77.3)	
Favipravir	*No*	12 (31.6)	10 (62.5)	2 (9.1)	***[b]0.001*****
	Yes	26 (68.4)	6 (37.5)	20 (90.9)	
Immune Modulatory Therapy	*No*	20 (52.6)	12 (75.0)	8 (36.4)	***[b]0.019****
	Yes	18 (47.4)	4 (25.0)	14 (63.6)	
Prone Positioning	*Yes*	19 (50.0)	13 (81.3)	6 (27.3)	***[b]0.001*****
	No	19 (50.0)	3 (18.8)	16 (72.7)	
$PEEP_{max}$ *(cm H2O)*	*Min-Max (Median)*	8-16 (12)	10-14 (12)	8-16 (12)	***[a]0.813***
	Mean±SD	11.53±2.15	11.63±1.67	11.45±2.48	
PIP_{max} *(cm H2O)*	*Min-Max (Median)*	15-45 (40)	30-45 (40)	15-45 (37.5)	***[c]0.099***
	Mean±SD	37.16±6.67	39.5±4.08	35.45±7.7	
PaO_2/FiO_2	*Min-Max (Median)*	40-130 (60)	50-80 (59)	40-130 (65)	***[c]0.094***
	Mean±SD	65.34±19.42	58.5±9.56	70.32±23.19	

N/L, neutrophil to lymphocyte ratio; CRP, C-reactive protein;ESR, Erythrocyte Sedimentation Rate; LDH, Lactate dehydrogenase; PEEP, Positive end-expiratory pressure;PIP, Peak inspiratory pressure, PaO2/FiO2, Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration; [a]Student-t Test, [b]PearsonChi-Square Test, [c]Mann Whitney U Test **p<0.01

Laboratory Parameters

In the evaluation of laboratory parameters, there was no statistically significant difference in $Hb_{min-max}$, Leu_{max}, N_{max}, L_{min}, , PLT_{max}, PLT_{min}, IL-6_{max}, CRP_{max}, D-$dimer_{max}$, LDH_{max}, $Ferritin_{max}$, $Procalsitonin_{max}$measurements between the groups (p>0.05) (Table 1). ESR_{max} and $Fibrinogen_{max}$ levels were found to be significantly higher in Group 1 (p= 0.001, p= 0.001; p<0.01). Secondary infection incidence and N/L_{max} ratios were lower in Group 1 than Group 2 (p=0.001, p=0.017; p<0.01, respectively). Secondary infectious agents included CMV, Candida sp., Staphylococcus sp., Klebsiella, Pseudomonas, Pneumocystis jirovecii, Enterobacter sp., and the most frequently isolated agent was Candida (Table 2).

Radiological Evaluation

All of Group 1 cases; 86.4% of Group 2 cases showed typical imaging findings, but no significant difference was found between the groups (p>0.05). The incidence of organizing pneumonia pattern, involvement of more than 75% of the lung parenchyma, and detection of diffuse distribution pattern were significantly higher in Group 1 (p=0.001, p<0.01) (Figure 1a,b,c). While organizing pneumonia pattern was observed in 87.5% of Group 1 cases; organizing pneumonia pattern was detected in only 22.7% of Group 2 cases (Figure 2a,b). According to the groups, no statistically significant difference was found in terms of unilateral/bilateral involvement of the cases, dominant infiltration pattern, dominant lobar distribution (upper lobe/ lower lobe), presence of pleural and pericardial effusion (p>0.05) (Table 3) (Figure 3,4,5).

Medical Treatment and Mechanical Ventilator Parameters

The rate of favipravir treatment, immune modulator treatment and prone position application in Group 1 cases was found to be statistically significantly lower than Group 2 (p=0.001; p=0.019; p=0.001, p<0.05). In addition, none of the Group 1 patients were treated with hydroxychloroquine and azithromycin.There was no significant difference between the groups in terms of $PEEP_{max}$, PIP_{max}, PaO2/Fio2 ratios (p>0.05) (Table 1).

The MV parameter values, comorbid diseases of the patients, which treatments were applied, and which infectious agents were produced are given in Table 2 in detail.

Table 2. Characteristics of patients in the ICU with and without pneumomediastinum

		Age	Hospitalization in the ICU (day)	ICU admission to PM interval (day)	IMV-PM interval (day)	Duration of IMV	Comorbidity	Treatment (Favipiravir)	Secondary infection	$PEEP_{max}$ ($cm H_2O$)	PIP_{max} ($cm H_2O$)	Min PaO_2/FiO_2	Immune Modulatory Therapy	Prone Position
Pneumomediastinum (+)	Case 1	60	25	10	7	22	-	-	-	12	40	50	-	-
	Case 2	59	12 (Alive)	9	2	5	-	Favipiravir	*CMV, Candida Albicans, Staphylococcus spp.*	10	40	58	pulse steroid (2x250mg 250 mg prednisone, 3 days)	-
	Case 3	74	40	30	25	35	HT	Favipiravir	*Stenotrophomonas Maltophilia, CMV, Candida Albicans*	10	35	50	pulse steroid (2x250mg 250 mg prednisone, 3 days)	-
	Case 4	44	15	9	5	11	-	Favipiravir	-	10	30	60	-	-
	Case 5	56	26	16	10	20	DM	-	-	14	45	60	-	-
	Case 6	58	23	10	9	22	-	-	-	12	40	58	-	-
	Case 7	71	37	26	26	37	HT	Favipiravir	*CMV, Candida Albicans, Pneumocystis carinii*	12	45	50	pulse steroid (2x250mg 250 mg prednisone, 3 days)	+
	Case 8	40	40	30	26	36	-	-	-	10	40	50	-	-
	Case 9	63	30	25	23	28	Lung CA	-	-	10	40	60	-	-
	Case 10	55	21	10	9	20	-	Favipiravir	-	10	35	60	-	-
	Case 11	54	40	30	30	40	HT, DM	-	-	12	40	60	-	-
	Case 12	31	46	35	29	40	-	-	-	14	45	50	-	-
	Case 13	16	36	30	10	16	Immunodeficiency	-	-	12	40	80	-	-
	Case 14	58	28	20	6	14	DM, Emphysema	-	-	14	42	100	-	-
	Case 15	57	20 (Alive)	15	1	6	DM	Favipiravir	-	10	40	120	-	+
	Case 16	67	27	12	1	16	Emphysema	-	*Stenotrophomonas Maltophilia, Pseudomonas Aeruginosa, Acinetobacter Baumannii, Staphylococcus spp.*	14	35	50	2x40mg prednisone	+
Pneumomediastinum (-)	Case 1	80	20			18	HT	Favipiravir	*Escherichia coli, Stenotrophomonas Maltophilia*	12	40	69	2x40mg prednisone	+
	Case 2	95	10			10	HT, DM	Favipiravir, Azithromyci, Hydroxychloroquine)	*Candida Albicans*	10	35	100	2x40mg prednisone	-
	Case 3	85	1			1		-	-	8	30	80		-
	Case 4	80	16			14	HT, DM, IHD, CeVD	-	*Klebsiella Pneumoniae, Candida spp., Staphylococcus spp.*	12	45	80	2x40mg prednisone	-
	Case 5	62	21			20	HT, DM	Favipiravir	-	8	40	130	2x40mg prednisone	-

Pneumomediastinum (-)	Case 6	54	19			15	İKH, HT	Favipiravir	*Acinetobacter Baumannii, Klebsiella Pneumoniae, Candida Albicans*	14	15	58	2x40mg prednisone	+
	Case 7	70	45			40	DM, HT, CeVD	Favipiravir	*Acinetobacter Baumannii, Klebsiella Pneumoniae, CMV*	10	25	65	2x40mg prednisone	+
	Case 8	60	18			18	HT, DM	Favipiravir	*Klebsiella Pneumoniae, Candida Albicans*	14	40	48	2x40mg prednisone	+
	Case 9	56	37			35	-	Favipiravir	*Stenotrophomonas Maltophilia, Staphylococcus spp.*	14	40	40	Anakinra, pulse steroid (2x250mg 250 mg prednisone, 3 days)	+
	Case 10	58	16			15	-	Favipiravir	*Candida Albicans*	12	35	55	2x40mg prednisone	+
	Case 11	69	38			35	COPD, HT, DM	Favipiravir	*Candida spp., Escherichia coli, Staphylococcus spp.*	12	30	65	2x40mg prednisone	+
	Case 12	75	60			58	HT, DM, OSAS	Favipiravir, Azithromyci, Hydroxychloroquine)	*Candida Albicans*	14	30	60	-	+
	Case 13	78	28			25	Atrial fibrillation	Favipiravir, Azithromyci, Hydroxychloroquine)	-	10	30	80	-	-
	Case 14	41	47			46	-	Favipiravir, Azithromyci, Hydroxychloroquine)	-	10	40	94	-	+
	Case 15	73	80			75	COPD, HT, İKH	Favipiravir	*Candida Albicans, Pseudomonas Aeruginosa*	8	45	50	-	+
	Case 16	70	53			52	HT,DM	Favipiravir, Azithromyci, Hydroxychloroquine)	*Candida Albicans*	14	45	69	2x40mg prednisone	+
	Case 17	55	32			31	Hyperlipidemia, Hypothyroidism	Favipiravir, Azithromyci, Hydroxychloroquine)	*Candida Albicans*	16	30	61	2x40mg prednisone	+
	Case 18	53	150			140	-	Favipiravir, Azithromyci, Hydroxychloroquine)	-	12	30	68	2x40mg prednisone	+
	Case 19	51	60			58	-	Favipiravir, Azithromyci, Hydroxychloroquine)	*Enterobacter cloacae*	14	40	50	-	+
	Case 20	77	25			22	Emphysema, COPD	Favipiravir, Azithromyci, Hydroxychloroquine)	*Klebsiella Pneumoniae*	8	45	55	-	+
	Case 21	59	33			30	DM	Favipiravir	*Staphylococcus spp., Candida spp.*	12	40	50	-	+
	Case 22	84	23			20	HT, DM, Parkinson	Favipiravir	*Acinetobacter Baumannii, Staphylococcus spp., Candida spp.*	8	30	120	Tocilizumab	-

ICU, Intensive care unit; IMV, Invasive mechanical ventilation; PM, pneumomediastinum; HT, Hypertension; DM, Diabetes Mellitus; CA, Cancer, IHD, Ischemic heart disease; PEEP, Positive end-expiratory pressure;PIP, Peak inspiratory pressure; CeVD, Cerebrovascular disease; OSAS, obstructive sleep apnea syndrome; COPD, Chronic obstructive pulmonary disease

Table 3. Radiological Findings by Presence of Pneumomediastinum

		Pneumomediastinum			
		Total (n=38)	Yes (n=16)	No (n=22)	p
		n (%)	n (%)	n (%)	
CT findings	**Typical**	35 (92.1)	16 (100.0)	19 (86.4)	[d]***0.249***
	atypical	3 (7.9)	0 (0.0)	3 (13.6)	
Organized pneumonia	**No**	19 (50.0)	2 (12.5)	17 (77.3)	[b]***0.001****
	Yes	19 (50.0)	14 (87.5)	5 (22.7)	
Percentage of Parenchymal Involvement	**1**	16 (42.1)	2 (12.5)	14 (63.6)	[e]***0.001****
	2	8 (21.1)	1 (6.3)	7 (31.8)	
	3	2 (5.3)	2 (12.5)	0 (0.0)	
	4	12 (31.6)	11 (68.8)	1 (4.5)	
Laterality	**Uniateral**	4 (10.5)	0 (0.0)	4 (18.2)	[d]***0.124***
	Bilateral	34 (89.5)	16 (100.0)	18 (81.8)	
Dominant infiltration pattern	**Ground-glass opacity**	20 (52.6)	7 (43.8)	13 (59.1)	[e]***0.402***
	Crazy-paving	14 (36.8)	8 (50.0)	6 (27.3)	
	Consolidation	4 (10.5)	1 (6.3)	3 (13.6)	
Dominant lobar distrubition	**Upper lobes**	7 (18.4)	1 (6.3)	6 (27.3)	[e]***0.053***
	Lower lobes	7 (18.4)	1 (6.3)	6 (27.3)	
	Diffuse	24 (63.2)	14 (87.5)	10 (45.5)	
Distribution	**Basal**	18 (47.4)	3 (18.8)	15 (68.2)	[e]***0.001****
	Central	3 (7.9)	0 (0.0)	3 (13.6)	
	Diffuse	17 (44.7)	13 (81.3)	4 (18.2)	
Pleural Effusion	**No**	26 (68.4)	10 (62.5)	16 (72.7)	[b]***0.503***
	Yes	12 (31.6)	6 (37.5)	6 (27.3)	
Pericardial Effusion	**No**	35 (92.1)	13 (81.3)	22 (100.0)	[d]***0.066***
	Yes	3 (7.9)	3 (18.8)	0 (0.0)	

CT, Computed tomography; [b]PearsonChi-Square Test [d]Fisher's Exact Test [e]Fisher Freeman Halton Test **p<0.01

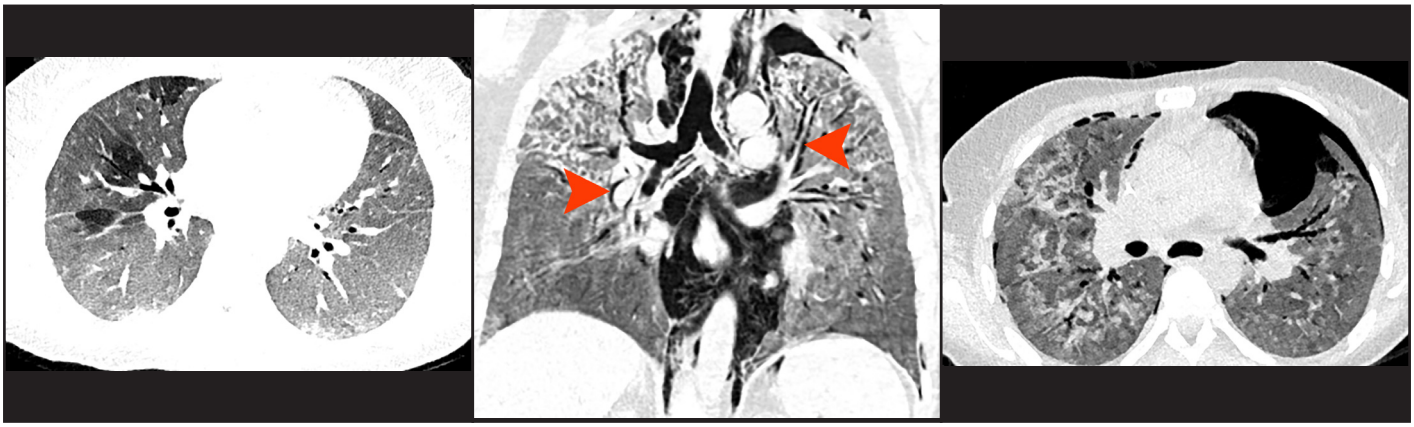

Figure 1. A 44-year-old female patient who developed pneumomediastinum and died while under mechanical ventilation support secondary to COVID-19 pneumonia. a; On thorax CT, it is seen that more than 75% of the lung parenchyma area is infiltrated. 1b; Pneumomediastinum developed on the 44th day during ICU hospitalization. Note that almost all lung parenchyma areas are infiltrated and perivascular free air images (red arrowhead). c; On the second control thorax CT obtained ten days later, it is seen that the pneumomediastinum still continues but is concentrated in the left hemithorax.

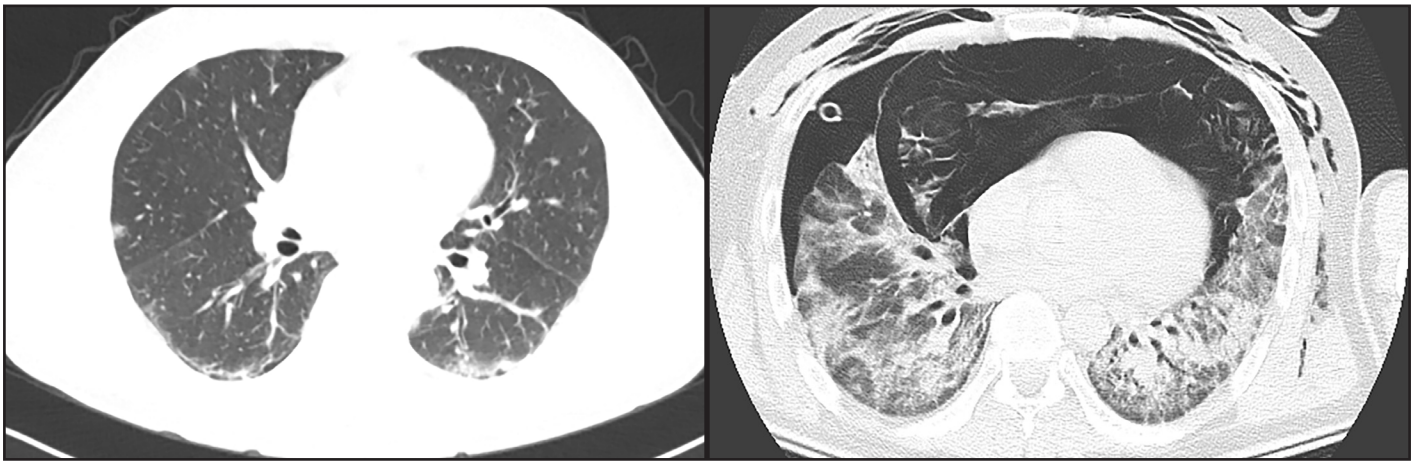

Figure 2. SARS-CoV-2 PCR(+), 40-year-old male patient,**a:** In the thorax CT examination taken at the first admission to outpatient on 25.10.2020, minimal infiltration is seen in the ground glass density, which shows a typical peripherobasal location for COVID-19 pneumonia in the bilateral lower and upper lobes of the lung. 10 days after this exam, the patient was taken to the intensive care unit due to the rapid deterioration of the clinical condition and the need for respiratory support. **b:** Extensive pneumomediastinum and subcutaneous emphysema are seen on thoracic CT in the patient under treatment in the ICU. The patient died 18 days after this exam.

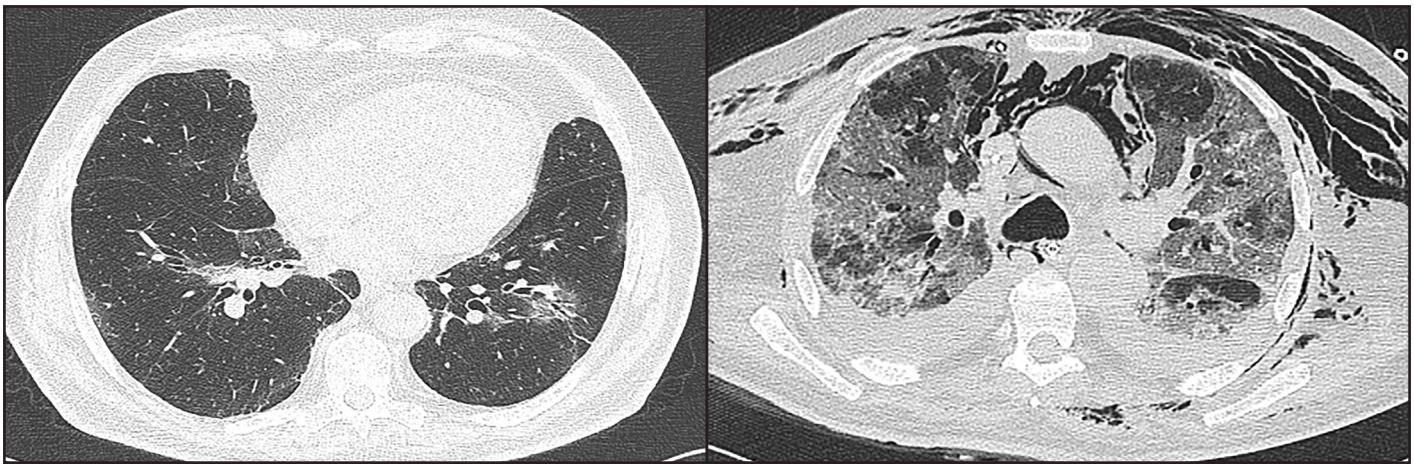

Figure 3. A 70-year-old male patient who developed pneumomediastinum and died due to COVID-19 pneumonia under mechanical ventilation in the ICU. **a:** Ground-glass opacities and minimal infiltration in crazy-paving pattern are seen in the lung parenchyma areas in thorax CT taken during outpatient admission dated 09.01.2021. **b:** On the thorax CT performed while under treatment in the ICU, 1 month after this exam, it is seen that infiltration, pneumomediastinum and subcutaneous emphysema develop an organized pneumonia pattern in which the lung parenchyma areas are almost completely affected. Note the bilateral pleural effusion.

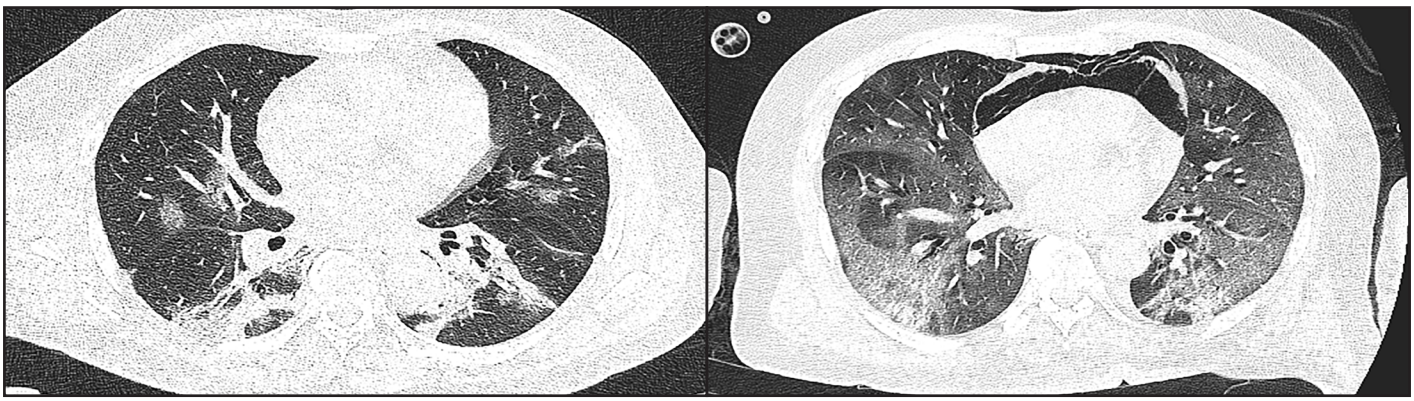

Figure 4. A 48-year-old male patient who developed pneumomediastinum during ICU hospitalization but was discharged without sequelae. **a:** Focal consolidations and minimal infiltrations in crazy-paving pattern are observed in thorax CT dated 13.04.2021. **b:** Minimal pneumomediastinum is seen on thorax CT taken under mechanical ventilation support in the ICU 6 days after this examination.

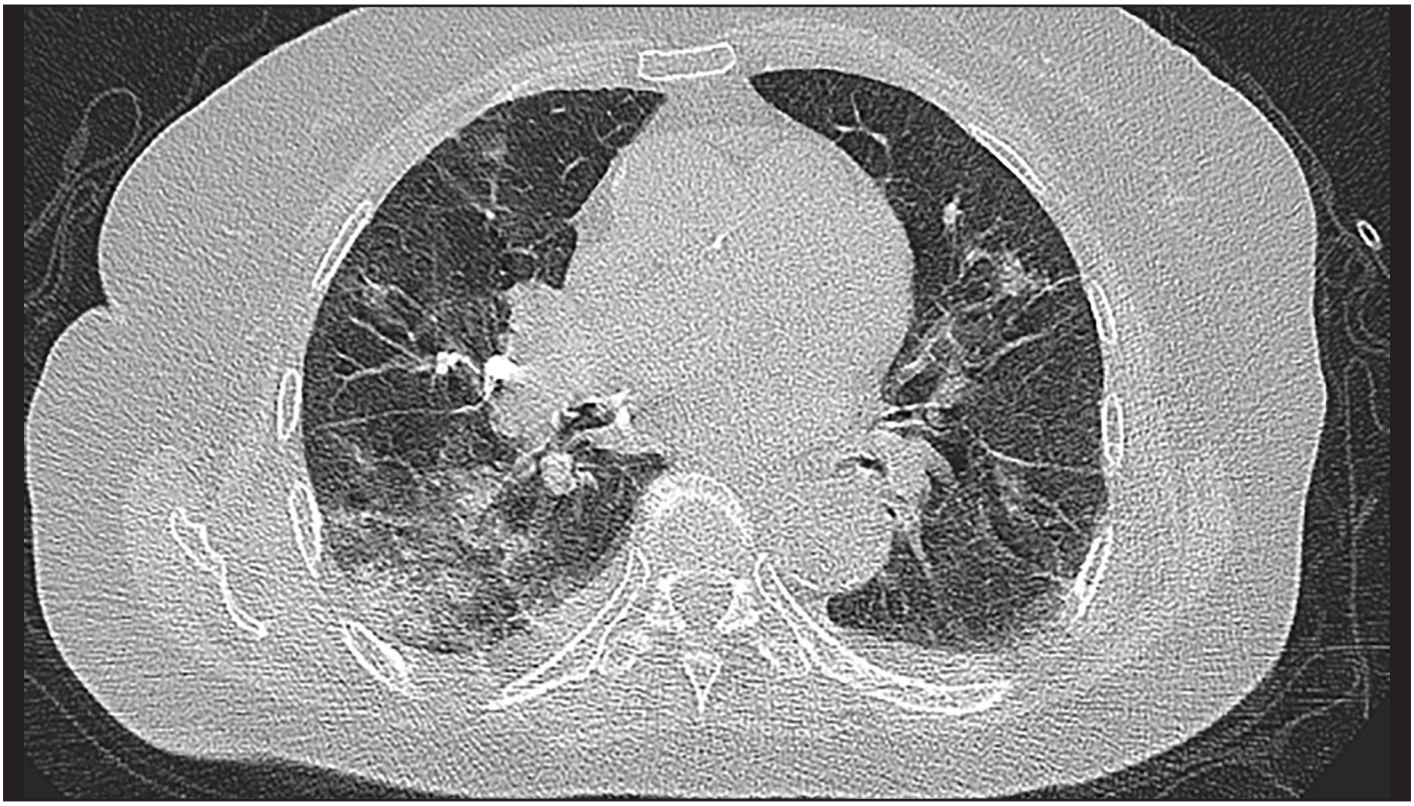

Figure 5. A 69-year-old female patient who stayed in the ICU for 38 days and received respiratory support for 35 days, but did not develop pneumomediastinum during her treatment, shows bilateral minimal pleural effusion and ground-glass parenchymal infiltrates on the thorax CT image. The patient died not because of respiratory failure, but because of secondary infections.

DISCUSSION

Although the mortality of COVID-19-associated pneumonia differeces in distinct countries, it is generally quite high compared to other infective agents [10]. Clinical outcomes of pneumonia due to COVID-19 is more severe in elderly, immunosuppressive, comorbid male patients who had secondary bacterial infection during COVID-19 [3,4,11]. Most of these patients need a short or long term mechanical ventilator during the course of the disease. It has been reported that mortality rates are higher in patients need mechanical ventilation support [3]. The timing of starting mechanical ventilation and duration is also important at this stage [12]. It has come to our attention that PM, which has a very mortal course, can develop in a small part of these patients under mechanical ventilator treatment. Although a definite reason has not been revealed yet, the most accepted thought is as the fragility of the alveolar mucosa as a result of the widespread damage caused by the virus in the alveoli, and the rupture of the alveoli by increasing the intraalveolar pressure with mechanical ventilation. This situations results with spreading the air to the mediastinum and subcutaneously along the perivascular spaces (Figure 1b, 3b) [5,13,14]. In other words, PM is the presence of air images in the intrathoracic and subcutaneous fatty planes caused by rupture of fragile airways with barotrauma (Figure 1c, 2b, 3b, 4b) [6]. While the rate of PM development due to MV in ARDS cases is around 6.5%; McGuinness et al. showed that patients with COVID-19 patients are more prone to barotrauma due to MV compared to ARDS cases developing secondary to other causes (Figure 1) [15,16]. Advanced PM produces an enormously increased intrathoracic pressure [17]. The major cause of mortality due to PM is explained as increased intrathoracic pressure leading to cardiac failure due to vascular return failure [17]. Most of the cases die as a result of cardiopulmonary arrest caused by increased intrathoracic pressure (Figure 1b,2b) [17]. However, while PM does not develop in the majority of cases treated with higher pressures, it is still a mystery that some patients develop PM even at low pressures. In this study, it was aimed to shed light on clinicians in the treatment process by determining possible risk factors or some predictive parameters for PM. According to the results of the study, It has been shown that male gender, advanced age, history of comorbid disease and the development of secondary infection during COVID-19 pneumonia, which

are accepted as risk factors for severe disease, are not a marker for PM. In fact, patients who developed PM were significantly younger than those who did not. When laboratory parameters were evaluated, it was shown that parameters such as D-Dimer, LDH, IL-6, CRP, and procalcitonin, which have prognostic value in severe disease, were not important for the prediction of PM [18,19].

When evaluated in terms of radiological parameters; it has been shown that cases with widespread involvement of the upper lobes in the form of crazy-paving and consolidation during COVID-19 pneumonia require more intensive care support [9]. Similarly, most of our cases showed these features radiologically, and all of them needed intensive care. However, diffuse infiltration of more than 75% of the total lung parenchyma area, including the central portions, especially in the organizing pneumonia pattern, was significantly higher in the PM group. Organized pneumonia is defined as the radiological appearance of exudate that occurs catastrophically with the inclusion of chronic inflammatory cells in the alveolar inflammation, mostly in the subacute-late period of the disease [20]. Alveolar epithelial cells become more fragile under this intense inflammation. For this reason, when exposed to high intraalveolar pressure such as the valsalva maneuver or mechanical ventilation, they are damaged immediately and patients enter hypoxemia very quickly [20,21]. As the result, the ventilation balance will be disturbed and the clinical picture results in acute respiratory distress syndrome (ARDS) [21]. Corticosteroid therapy, which is started in these patients in the early period, is often life-saving by suppressing inflammatory cells [20,21]. In our study, the presence of typical/atypical imaging findings in terms of COVID-19, ground glass opacities/crazy-paving/consolidation infiltration pattern, upper-lobe involvement, pleural-pericardial effusion did not differ significantly in terms of development of PM.

Many medical treatments such as chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir, remdesivir, and ivermectin have been tried against the SARS-CoV-2 viral agent since the early period of the pandemic [10]. However, it has been shown that favipiravir treatment provides faster clinical improvement by rapid viral clearance, therefore, it is more effective than other drugs and can be used safely in the treatment of COVID-19 [22]. In our study, the rates of receiving favipiravir treatment were significantly lower in patients who developed PM. Perhaps, if favipiravir had been started in these patients in the early stages of the disease, the virus would have been controlled easily and quickly. So that ARDS would not have occurred and PM would not have been developed since it would not have exacerbated the systemic and alveolar inflammatory response too much. Again, immunomodulatory treatments such as tocilizumab and IL antagonists, especially corticosteroids, have been used extensively in the treatment of COVID-19 to suppress cytokine release and complications caused by cytokine storms [23,24]. In our study, the use of immunomodulatory therapy was significantly lower in the PM group. We think that this situation may increase cytokine-dependent alveolar damage and pave the way for PM.

We mentioned that the main mechanism responsible for the development of COVID-19-associated PM is barotrauma caused by mechanical ventilation on the basis of alveolar damage. Mortality rates increase in intubated COVID-19 patients with or without PM [25]. Therefore, patient selection for intubation is critical [25]. Intubation time is also important, and early respiratory therapy in critically ill patients increases surveillance [26]. However, in cases where the cytokine storm is heavy, one should be very controlled when adjusting the pressure values. Because a small pressure change to balance blood oxygenation may result in PM, a complication with very high mortality. In our study, no significant difference was found between the two groups in terms of MV parameters such as $PEEP_{max}$ and PIP_{max}. In this case, the following questions comes to mind: Why PM developed in patients whose intraalveolar pressure was not higher than other patients? Are the other factors rather than barotrauma due to mechanical ventilation more important for the development of PM? Although the answer is yes according to the results of this study, further studies with larger series are needed.The fact that there was no statistically significant difference between groups in terms of the duration of ICU hospitalization and mechanical ventilation time between the groups supports this hypothesis.

Limitations

Our single-center retrospective study has some limitations. The most important limitation is the small number of patients for both groups. However, the number of PM cases for a single center is considerably higher than similar examples in the literature, although it is actually regrettable. Since the medical treatments used for the treatment of COVID-19 in our hospital are limited, favipiravir is primarily mentioned in the study. The relationship between other medical treatments and PM may also be a subject for other studies. Since the cases in our study

had only single CT images, radiological evaluations were made with the available images. This may be considered as another limitation of the study.On the other hand, we think that this study is important because it is the first study to systematically evaluate pneumomediastinum, which is considered the most mortal complication of COVID-19 pneumonia, in all aspects. Although this was not the case in our hospital, intensive care specialists in most hospitals could not keep up with the incredible need for intensive care during the pandemic. During this period, intensive care patients were often followed by physicians from other specialities. However, especially patients with respiratory distress or deterioration in general condition were admitted to intensive care. We think that we can ignore this situation since almost all patients with COVID-19-related or intubation-related pneumomediastinum need intensive care.

CONCLUSION

As the result; the probability of PM which is a very rare condition in the course of COVID-19 pneumonia, is high in patients who have diffusely organizing pneumonia pattern, and those affected more than 75% of the total lung volume. In these patients, immunomodulatory and antiviral therapy and prone position should be started early, and damage at the alveolar level should be minimized. Thus, it may be possible to prevent pneumomediastinum, the most mortal complication of COVID-19 pneumonia.

Conflict of interest: The authors declare that there is no conflict of interest

Informed Consent: Patients were not required to give their informed consent for inclusion in this retrospective study, because we used anonymous clinical data and individual cannot be identified according to the data present.

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Availability of Data and Materials: The materials described in the manuscript will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Ethics Approval: The study protocol was approved by Acibadem University Clinical Research Ethics Committee (Date: 2021-03-10, Approval number: 2021-05/03). The study complied with the Declaration of Helsinki.

Author Contributions: Concept – D.E.T.S., E.G., D.Y.; Design - D.E.T.S., E.G., D.Y., C.E.K., O.D., I.O.A.; Supervision – D.E.T.S., C.E.K., D.Y., O.D., I.O.A.; Resource - D.E.T.S., E.G., N.E., S.K., I.D., A.N.S.; Materials - D.E.T.S., E.G., N.E., S.K., I.D., A.N.S.; Data Collection and/or Processing - D.E.T.S., E.G., N.E., S.K., I.D., A.N.S.; Analysis and/or Interpretation - D.E.T.S., E.G., N.E., S.K., I.D., A.N.S.; Literature Search - D.E.T.S., A.N.S.; Writing - D.E.T.S.; Critical Reviews - D.E.T.S., D.Y., C.E.K., O.D., I.O.A.

REFERENCES

[1] Johansson MA, Quandelacy TM, Kada S, Prasad PV, Steele M, Brooks JT, et al. (2021) SARS-CoV-2 transmission from people without COVID-19 symptoms. JAMA network open. 4(1):e2035057. https://doi.org/10.1001/jamanetworkopen.2020.35057

[2] Fajgenbaum DC, June CH. (2020) Cytokine Storm. N Engl J Med. 383(23):2255-2273. https://doi.org/10.1056/NEJMra2026131

[3] Luo M, Cao S, Wei L, Zhao X, Gao F, Li S, et al. (2020) Intubation, mortality, and risk factors in critically ill Covid-19 patients: A pilot study. J Clin Anesth. 67:110039. https://doi.org/10.1016/j.jclinane.2020.110039

[4] Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. (2020) China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 55(5):2000547. https://doi.org/10.1183/13993003.00547-2020

[5] Elhakim TS, Abdul HS, Pelaez Romero C, Rodriguez-Fuentes Y. (2020) Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema in COVID-19 pneumonia: a rare case and literature review. BMJ Case Rep. 13(12):e239489. https://doi.org/10.1136/bcr-2020-239489

[6] Kangas-Dick A, Gazivoda V, Ibrahim M, Sun A, Shaw JP, Brichkov I, et al. (2021) Clinical Characteristics and Outcome of Pneumomediastinum in Patients with COVID-19 Pneumonia. J Laparoendosc Adv Surg Tech A. 31(3):273-278. https://doi.org/10.1089/lap.2020.0692

[7] Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. (2020) Radiological Society of North America Expert Consensus Document on Reporting Chest CT Findings Related to COVID-19: Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA. Radiol Cardiothorac Imaging. 2(2):e200152. https://doi.org/10.1148/ryct.2020200152

[8] Pogatchnik BP, Swenson KE, Sharifi H, Bedi H, Berry GJ, Guo HH. (2020) Radiology-Pathology Correlation Demonstrating Organizing Pneumonia in a Patient Who Recovered from COVID-19. Am J Respir Crit Care Med. 202(4):598-599. https://doi.org/10.1164/rccm.202004-1278IM

[9] Tekcan Sanli DE, Yildirim D, Sanli AN, Erozan N, Husmen G, Altundag A, et al. (2021) Predictive value of CT imaging findings in COVID-19 pneumonia at the time of first-screen regarding the need for hospitalization or intensive care unit. Diagn Interv Radiol. 27(5):599-606. https://doi.org/10.5152/dir.2020.20421

[10] Simsek EE, Guner AE, Kul S, Karakurt Z, Tekesin K, Birinci S. (2020) A comparative analysis of the COVID-19 pandemic response: The case of Turkey. North Clin Istanb. 7(5):443-451. https://doi.org/10.14744/nci.2020.87846

[11] Jordan RE, Adab P, Cheng KK. (2020) Covid-19: risk factors for severe disease and death. BMJ. 368:m1198. https://doi.org/10.1136/bmj.m1198

[12] Meng L, Qiu H, Wan L, Ai Y, Xue Z, Guo Q, et al. (2020) Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. Anesthesiology. 132(6):1317-1332. https://doi.org/10.1097/ALN.0000000000003296

[13] Ghani M, Rodriguez-Ortiz Y, Ahmad D, Pham J, Tamsukhin P, Mir P. (2020) Spontaneous pneumomediastinum in patients with SARS-Cov-2 virus (COVID-19). Chest. 158(4):A1231-2. https://doi.org/10.1016/j.chest.2020.08.1121

[14] Kolani S, Houari N, Haloua M, Alaoui Lamrani Y, Boubbou M, Serraj M, et al. (2020) Spontaneous pneumomediastinum occurring in the SARS-COV-2 infection. IDCases. 21:e00806. https://doi.org/10.1016/j.idcr.2020.e00806

[15] Anzueto A, Frutos-Vivar F, Esteban A, Alía I, Brochard L, Stewart T, et al. (2004) Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. Intensive Care Med. 30(4):612-9. https://doi.org/10.1007/s00134-004-2187-7

[16] McGuinness G, Zhan C, Rosenberg N, Azour L, Wickstrom M, Mason DM, Thomas KM, Moore WH. (2020) Increased Incidence of Barotrauma in Patients with COVID-19 on Invasive Mechanical Ventilation. Radiology. 297(2):E252-E262. https://doi.org/10.1148/radiol.2020202352

[17] Wali A, Rizzo V, Bille A, Routledge T, Chambers AJ. (2020) Pneumomediastinum following intubation in COVID-19 patients: a case series. Anaesthesia. 75(8):1076-1081. https://doi.org/10.1111/anae.15113

[18] Sanli DET, Altundag A, Kandemirli SG, Yildirim D, Sanli AN, Saatci O, et al. (2021) Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia. Am J Otolaryngol. 42(1):102796. https://doi.org/10.1016/j.amjoto.2020.102796

[19] Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. (2020) Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta. 510:475-482. https://doi.org/10.1016/j.cca.2020.08.019

[20] de Oliveira Filho CM, Vieceli T, de Fraga Bassotto C, da Rosa Barbato JP, Garcia TS, Scheffel RS. (2021) Organizing pneumonia: A late phase complication of COVID-19 responding dramatically to corticosteroids. Braz J Infect Dis. 25(1):101541. https://doi.org/10.1016/j.bjid.2021.101541

[21] Kory P, Kanne JP. (2020) SARS-CoV-2 organising pneumonia: 'Has there been a widespread failure to identify and treat this prevalent condition in COVID-19?'. BMJ Open Respir Res. 7(1):e000724. https://doi.org/10.1136/bmjresp-2020-000724

[22] Manabe T, Kambayashi D, Akatsu H, Kudo K. (2021) Favipiravir for the treatment of patients with COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 21(1):489. https://doi.org/10.1186/s12879-021-06164-x

[23] Zhao M. (2020) Cytokine storm and immunomodulatory therapy in COVID-19: Role of chloroquine and anti-IL-6 monoclonal antibodies. Int J Antimicrob Agents. 55(6):105982. https://doi.org/10.1016/j.ijantimicag.2020.105982

[24] Alijotas-Reig J, Esteve-Valverde E, Belizna C, Selva-

O'Callaghan A, Pardos-Gea J, Quintana A, et al. (2020) Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. Autoimmun Rev. 19(7):102569. https://doi.org/10.1016/j.autrev.2020.102569

[25] van der Veer T, van der Sar-van der Brugge S, Paats MS, van Nood E, de Backer IC, Aerts JGJV, et al. (2021) Do-not-intubate status and COVID-19 mortality in patients admitted to Dutch non-ICU wards. Eur J Clin Microbiol Infect Dis. 40(10):2207-2209. https://doi.org/10.1007/s10096-021-04223-4

[26] Zirpe KG, Tiwari AM, Gurav SK, Deshmukh AM, Suryawanshi PB, Wankhede PP, et al. (2021) Timing of Invasive Mechanical Ventilation and Mortality among Patients with Severe COVID-19-associated Acute Respiratory Distress Syndrome. Indian J Crit Care Med. 25(5):493-498. https://doi.org/10.5005/jp-journals-10071-23816

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