

# Should Pneumothorax Developing During the Recovery Period After COVID-19 in Patients with Previously Healthy Lungs be Considered a Primary Spontaneous Pneumothorax or a Secondary Spontaneous Pneumothorax?

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## Abstract

**OBJECTIVE:** It is still unknown how to call the pneumothorax that develops during the recovery period after coronavirus disease 2019. Patients who developed pneumothorax during the recovery period after coronavirus disease 2019 were compared with those who had a primary or secondary spontaneous pneumothorax without a coronavirus disease 2019 history.

**MATERIAL AND METHODS:** Between 2020 and 2021, 160 patients with pneumothorax were retrospectively analyzed. Twenty-three patients had a history of coronavirus disease 2019 (coronavirus disease recovery) confirmed by real-time reverse transcriptase-polymerase chain reaction, whereas the remaining 137 patients did not have a history of coronavirus disease 2019 (18 of the patients with secondary spontaneous pneumothorax group and 119 patients with primary spontaneous pneumothorax group).

**RESULTS:** The median time between discharge and readmission to the hospital because of pneumothorax was 9 days in the coronavirus disease recovery group. There were statistically significant differences in regards to age ( $P < .001$ ), gender ( $P = .02$ ), the presence of bullae ( $P = .02$ ), and dystrophic severity lung score ( $P = .04$ ) between the coronavirus disease recovery and primary spontaneous pneumothorax groups, whereas no difference was found between the coronavirus disease recovery and the secondary spontaneous pneumothorax groups ( $P > .05$ ). The prolonged air leak was observed in 17.6% ( $n = 25$ ). Patients who had prolonged air leak were statistically higher in the coronavirus disease recovery group than the primary spontaneous pneumothorax group (56.5% vs. 10.1%), although it was almost similar between the coronavirus disease recovery and secondary spontaneous pneumothorax groups ( $P = .951$ ). On logistic regression analysis, the coronavirus disease recovery group was the independent factor for prolonged air leak (odds ratio = 9.900, 95% CI = 1.557-62.500,  $P = .01$ ).

**CONCLUSION:** Pneumothorax may be developed during the recovery period after coronavirus disease 2019 in patients with previously healthy lungs, and it should be called as secondary spontaneous pneumothorax.

**KEYWORDS:** Thoracic surgery, SARS-CoV-2, recovery, pneumothorax, primary, secondary

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of the coronavirus disease 2019 (COVID-19), is associated with pneumothorax (PNMX).<sup>1</sup> The incidence of PNMx (either spontaneous or ventilation-related) was reported between 0.6% and 19% in the COVID-19 pandemic, and it was related to high mortality and morbidity.<sup>2-5</sup> Since the patients examined in the published studies show different changes such as follow-up in the intensive care unit (ICU) or not, is connected to mechanical ventilation (MV), and the degree of parenchymal involvement, the incidence of PNMx is varied so much. Although there are many studies about PNMx as a consequence of COVID-19, the delayed occurrence of PNMx in the follow-up after recovery from the infection is less commonly reported.<sup>6-10</sup> Pneumothorax may develop during the recovery period after COVID-19 since it was observed that the lungs of patients with COVID-19 showed distinctive vascular features, consisting of severe endothelial injury associated with the disrupted cell membranes in an autopsy study.<sup>11</sup> Patients who had PNMx in the follow-up after recovery from COVID-19 can be previously healthy without any risk factors as well as those who have received positive pressure ventilation caused by COVID-19 pneumonia.<sup>9,10</sup>

To the best of our knowledge, the present study has the largest number of patients with PNMx developing during recovery from COVID-19, and there was no study that investigated whether PNMx developing during recovery from COVID-19 is primary or secondary spontaneous PNMx yet.

In the present study, we aimed to compare patients who developed PNMx during the recovery period after COVID-19 with those who had primary or secondary spontaneous PNMx without a COVID-19 history.

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## MATERIALS AND METHODS

The present study was approved by the ethics committee of the Bakirköy Dr. Sadi Konuk Research and Education Hospital (2022–53).

### Patients

Between January 01, 2021, and January 01, 2022, a retrospective analysis was performed on 220 patients with a PNMX in our center. Patients who develop PNMX when being treated in the ward and/or ICU for COVID-19 pneumonia (n = 52) were excluded because it is not known whether the disease itself or a treatment such as MV caused PNMX. Patients with a history of an underlying pulmonary pathology that alters normal lung structure who developed a PNMX during the recovery period after COVID-19 (n = 5) were excluded. Because it was not known whether changes in the lung parenchyma were caused by COVID-19 pneumonia or an underlying pulmonary pathology cause PNMX. Pneumothorax patients with COVID-19 who were discharged from hospital more than 4 weeks ago (n = 3) were also excluded, since the recovery period from COVID-19 is considered to be a maximum of 4 weeks in the published studies.<sup>6,7</sup>

There were 23 PNMX patients who had a history of confirmed COVID-19 by the real-time reverse transcriptase-polymerase chain reaction and were discharged with healing from the hospital less than 4 weeks ago (COVID-recovery group), and they had no major risk factors for spontaneous PNMX in their medical history. A total of 137 PNMX patients did not have a history of COVID-19 (non-COVID group). The non-COVID group was divided into 2 subgroups: primary spontaneous PNMX (PSP group, n = 119) and secondary spontaneous PNMX (SSP group, n = 18). Secondary spontaneous pneumothorax was considered as PNMX developing in patients with an underlying pulmonary pathology that alters normal lung structure.

### *Pneumothorax Volume Estimation, Sub-analysis for Dystrophic Lesions, and Total Lung Severity Score*

For all patients, the first chest radiograph confirming the diagnosis of PNMX was carefully reviewed and was used to quantify the volume of the PNMX. It was calculated using the formulas in the same manner as described elsewhere: volume =  $4.2 + [4.7 \times (A+B+C)]$ .<sup>12</sup> In this method, A+B+C is

defined as the sum of interpleural distances in the case of PNMX. The pulmonary bullae were considered as a lesion with no discernible wall which measures more than 1-2 cm in diameter, whereas the pulmonary bleb was considered as a lesion less than 1 cm. The ipsilateral dystrophic severity score (DSS) was calculated with a chest computed tomography (CT) based on the type, distribution, and the number of dystrophic lung lesions.<sup>13</sup>

For each of the 23 patients in the COVID-recovery group, visual CT was evaluated on the admission to the hospital, and the percentage of involvement in each lobe, as well as the overall lung “total severity score (TSS),” was recorded. According to the TSS, patients were classified as none (0%), minimal (1%-25%), mild (26%-50%), moderate (51%-75%), or severe (76%-100%).

### Statistical Analysis

The data were entered into the Statistical Package for the Social Sciences (IBM SPSS 14 Statistics for Windows, Version 23.0, Armonk, NY, USA). Descriptive statistics were used to summarize pertinent study information. It was decided whether the distributions were normal or not by Kolmogorov–Smirnov analysis. Quantitative variables are presented as mean, maximum (max), and minimum (min) values and qualitative variables are presented as percentage values. The Student’s *t*-test was used for comparisons between the groups. The Pearson’s chi-squared test was used for the analysis of qualitative variables; however, the Fisher’s exact test was used if the sample size was small. Anormal distributions were reported as median and interquartile range (IQR) values. Non-parametric continuous variables, presented as median values, were compared using the Mann–Whitney *U* test. To determine the independent risk factors affecting the prolonged air leak, logistic regression analysis (multivariate analysis) was performed using the variables. Statistical significance was set at  $P < .05$ .

## RESULTS

In the COVID-recovery group, 15 patients were treated in the ward, whereas 8 patients were admitted to ICU (5 of them were invasively ventilated and the remaining 3 patients were supported by non-invasive mechanical ventilation). According to the TSS, patients in the COVID-recovery group were classified as none (n = 1), minimal (n = 9), mild (n = 6), moderate (n = 6), or severe (n = 1) at the first hospitalization. When the CT scans of the patients at the time of diagnosis of COVID-19 were examined, no bullae were observed in the chest x-ray of any patient. The median time between discharge and readmission to the hospital because of PNMX was 9 days (min = 2, max = 27 days, IQR = 18) in the COVID-recovery group.

The demographic, clinical, and radiological data of the patients are shown in Table 1.

There were no significant differences in regards to smoking ( $P = .142$ ), the type of treatment for PNMX ( $P = .771$ ), and the side of PNMX ( $P = .685$ ) between the COVID-recovery group and the PSP group.

### MAIN POINTS

- Pneumothorax can be observed in the follow-up after recovery from the coronavirus disease 2019 (COVID-19) due to pulmonary sequelae of the disease.
- Pneumothorax should be kept in mind in patients recovering from COVID-19 in case of sudden-onset progressive dyspnea, and it is not related to the initial severity of COVID-19.
- Pneumothorax developed during the recovery period after COVID-19 in patients with previously healthy lungs should be considered as a secondary spontaneous pneumothorax.

**Table 1.** Demographic/Radiological Data of Patients

Variables	COVID-Recovery Group (n = 23)	SSP Group (n = 18)	PSP Group (n = 119)	<i>P</i> <sup>1</sup>	<i>P</i> <sup>2</sup>
Age, median year (IQR)	55.0 (13.0)	54.5 (12.2)	22.0 (10.0)	.979	<b>&lt;.001</b>
Gender, n/%					<b>.02</b>
Female	5/21.7	2/11.1	7/5.9	.438	
Male	18/78.3	16/88.9	112/94.1		
Smoking, n/%	12/52.2	12/66.7	81/68.1	.350	.142
Cigarette, median pack/years	12.0 (3.0)	15.5 (10.0)	6.0 (7.0)	.08	.09
Type of treatment, n/%					<b>.711</b>
Conservative	3/13.0	2/11.1	12/10.1%	1.000	
Chest tube	20/87.0	16/88.9	107/89.9		
Side, n/%					<b>.685</b>
Left	9/39.1	7/38.9	52/43.7	.987	
Right	14/60.9	11/61.1	67/56.3		
Collins volume, median % (IQR)	34.0 (17.0)	33.2 (17.6)	40.4 (57.0)	.906	.06
Presence of bleb (smaller than 1cm), n/%	2/11.1	4/17.4	42/35.3	.679	.143
Presence of bullae (larger than 1cm), n/%	10/43.5	9/50.0	25/21.0	.678	<b>.02</b>
DSS grade, median (IQR)	4.0 (5.0)	5.0 (1.2)	3.0 (4.0)	.128	<b>.04</b>

<sup>1</sup>COVID-recovery group versus SSP; <sup>2</sup> COVID-recovery group versus PSP.

DSS, dystrophic severity score; n, number; IQR, interquartile range; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax. (Boldface indicates statistical significance).

Patients in the COVID-recovery group were older than patients in the PSP group ( $P < .001$ ). There were more female patients in the COVID-recovery group than the PSP group, and this difference was statistically significant ( $P = .02$ ). There was no statistical difference in terms of the presence of bleb between the COVID-recovery group and the PSP group ( $P = .143$ ), although the number of patients with bullae was higher in the COVID-recovery group than in the PSP group ( $P = .02$ ). Dystrophic severity score in patients in the COVID-recovery group was statistically higher than those in the PSP group ( $P = .04$ ).

There was a trend toward statistical significance in Collins volume ( $P = .06$ ) and use of cigarette packs/years ( $P = .09$ ) between the COVID recovery and the PSP groups. Compared to the PSP group, the volume of PNMx was less in the COVID-recovery group (median PNMx volume was 34.0% in the COVID-recovery group and 40.4% in the PSP group). Patients in the COVID-recovery group had more use of cigarette packs/year than those in the PSP group.

There were no significant differences in terms of all variables between the COVID-recovery group and the SSP group.

Prolonged air leak was observed in 17.6% ( $n = 25$ ) of the patients. Patients who had prolonged air leak were statistically higher in the COVID-recovery group than the PSP group (56.5% vs. 10.1%,  $P < .001$ , odds ratio = 11.627, 95% CI = 4.184-32.258), although it was almost similar between the COVID-recovery and SSP groups (56.5% vs. 55.6%,  $P = .951$ , odds ratio = 1.040, 95% CI = 0.300-3.603). On logistic regression analysis, COVID recovery and SSP groups

were the independent factors affecting prolonged air leak (Table 2).

The median length of stay in the hospital was 7 days (min = 1, max = 36 days, IQR = 7.0) in the COVID-recovery group, whereas it was 6 days (min = 1, max = 17 days, IQR = 6.0) in the PSP group and 8 days in the SSP group (min = 2, max = 29, IQR = 9.5) (PSP vs. COVID recovery,  $P = .06$ , and SSP vs. COVID-recovery,  $P = .722$ ).

**Table 2.** Factors Affecting Prolonged Air Leak with Logistic Regression Analysis

Variables	OR	95%CI	<i>P</i>
Age (per year)	1.000	0.951-1.051	.998
Gender (male vs. female)	1.294	0.246-6.789	.761
Side (right vs. left)	0.905	0.330-2.483	.846
Collins PNMx volume (per volume)	1.003	0.990-1.017	.639
Bullae/blep (no vs. yes)	0.532	0.039-07.217	.532
DSS (per score)	1.394	0.821-2.366	.219
<b>Group</b>			
PSP (reference)	1		
SSP	5.347	1.223-34.482	<b>.04</b>
COVID recovery	9.900	1.557-62.500	<b>.01</b>

DSS, dystrophic severity score; OR, odds ratio; PSP, primary spontaneous pneumothorax; SSP, secondary spontaneous pneumothorax. (Boldface indicates statistical significance).

## DISCUSSION

The COVID-19 pandemic is responsible for several hospitalizations worldwide and is characterized by wide heterogeneity in clinical presentation.<sup>14</sup> There is still a lack of knowledge about the short- and long-term consequences of COVID-19.<sup>15</sup> Although PNMX is a rare complication seen in patients with SARS-CoV-2 infection, there was an increase in the incidence of PNMX in patients with confirmed COVID-19.<sup>2-5</sup> Data on the incidence and outcomes of PNMX during the COVID-19 pandemic were published in large-scale studies although a review of them shows that PNMX is scarcely reported after the recovery from the illness. However, PNMX can occur during different phases of illness even in patients without a history of lung disease.<sup>6,8</sup> Patients who have no major risk factors for spontaneous PNMX in their medical history, or who were not intubated or even hospitalized at the time of COVID-19 infection, may develop PNMX during recovery from COVID-19.<sup>6-10</sup> It means that PNMX complication is still possible even after the infection has been overcome.

Since there are only case report studies on patients who develop PNMX during recovery from COVID-19, there is still no consensus regarding the acceptance of these patients as PSP or SSP. While some cases who develop PNMX during recovery from COVID-19 were followed up as PSP, some of them were accepted as SSP in the literature.<sup>7,8,10,16</sup> To the best of our knowledge, the present study is the first study that compared PSP and SSP patients with those who develop PNMX during recovery from COVID-19. It was found that patients who develop PNMX during recovery from COVID-19 should be considered as SSP in the current study. According to published studies, COVID-19 pneumonia results in diffuse alveolar damage, inflammation of alveolar septa, necrosis of pneumocytes, fibrosis, giant bullae, and pneumatoceles.<sup>8,9,17,18</sup> Since the duration of all these conditions in the recovery period is unknown, they may contribute to PNMX in the recovery period of COVID-19. It supports the acceptance of post-COVID-19 PNMX as SSP.

In a post-mortem study, it was found that pneumocytes that are identified as the synthesizing cells of the alveolar surfactant, which has important properties in maintaining alveolar and airway stability pneumocytes, were lost from multifocal (53%) to diffuse level (19%).<sup>18</sup> In COVID-19 patients, it is possible that the process of parenchymal destruction that will result in PNMX continues with a longer duration of illness.<sup>9</sup> In the present study, the median time between discharge and readmission to the hospital because of PNMX was 9 days. Therefore, in case sudden respiratory symptoms appear after discharge in patients who have overcome the active infection, PNMX should be kept in mind. On the other hand, the minimal to severe COVID-19 pulmonary involvement at first baseline in patients in the COVID-recovery group indicates that PNMX is not related to the initial severity of COVID-19.

It was observed that the rate of emphysema-like anomalies (bullae or blebs) was different between the 3 groups. The presence of bullae that was one of the emphysema-like anomalies was higher in the COVID-recovery group than in

the PSP group although there was no significant difference between the COVID-recovery and SSP groups. A bullae formation can develop where first ground-glass opacities had been observed in COVID-19 patients.<sup>16,19</sup> It was hypothesized that pathological findings associated with COVID-19 pneumonia such as diffuse alveolar damage, inflammation of alveolar septa, and necrosis of pneumocytes may lead to bullae formation thereby predisposing to PNMX in different stages of illness.<sup>16,18</sup> When the chest CT scans of the patients performed at the time of the diagnosis of COVID-19 were examined, no bullae were observed; however, there was development of bullae formation in the follow-up of these patients. This situation supports the hypothesis described above. Although the information of the lung parenchyma of COVID-19 patients about the pre-COVID-19 period was not available, the rate of bullae in the COVID-recovery group in the present study was 43.5%. The prevalence of emphysema-like anomalies was reported between 6% and 15% among a small group of healthy persons.<sup>20,21</sup> Although the patients in these studies were not comparable with those in the current study, it is seen that emphysema-like anomalies are high in patients in the COVID-recovery group.

Although patients in the COVID-recovery group have previous healthy lungs, prolonged air leak was more common in these patients. When looking at the published studies, it has been reported that a PNMX developing both during the COVID-19 pneumonia period and during the recovery period of disease causes prolonged air leak.<sup>22-24</sup> There are different hypotheses about this. First, a prolonged air leak is developed due to the persistent chronic inflammatory changes and a delayed alveolar breach as part of an ongoing chronic disease process.<sup>23</sup> Second, focal endothelitis may cause prolonged healing in the lung parenchyma.<sup>24</sup> Patients in the COVID-recovery group have higher DSS than those with PSP; this supports the hypotheses of the prolonged air leak. On the other hand, it should be noted that it may represent sequelae of COVID-19.<sup>17</sup>

## Limitations

There were some limitations in the present study. First, it was a single-center and retrospective study. However, due to being a single-center study, it can be claimed that it has achieved a standard in treatment approaches. Second, although it was accepted that patients were previously healthy lungs, it should be kept in mind that their history of pulmonary disease may have emerged with COVID-19. However, it is impossible to calculate the probability of patients developing PNMX if they did not catch COVID-19. Third, the rate of PNMX patients in the COVID-recovery group (10.4%) seems to be high. It can be attributed to the fact that our hospital serves as a pandemic hospital.

The present study also has a few strong points. First, the present study is known to be the first study to compare the outcomes of PSP, SSP, and COVID-19-recovery PNMX groups. Second, the authors' institutions are the largest-volume centers that take care of patients with COVID-19 and PNMX in Istanbul, and it can be said that treatment and follow-up quality have been highly standardized throughout the study period.



## CONCLUSION

Pneumothorax may develop in previously healthy lungs during the recovery period from COVID-19, and it is not related to the initial severity of COVID-19. It should be kept in mind in patients recovering from COVID-19 in case of sudden-onset progressive dyspnea. Although the short-term follow-up showed the pulmonary sequelae of COVID-19 and the risk of PNMx in patients with a COVID-19 history, prospective studies with long-term follow-up of COVID-19 patients are needed to provide enough knowledge about the relationship between the recovery period of COVID-19 and PNMx. The underlying mechanisms responsible for PNMx in patients in the recovery period of COVID-19 should be investigated with further research. Pneumothorax developed during the recovery period after COVID-19 in patients with previously healthy lungs should be considered as a secondary spontaneous pneumothorax.

**Ethics Committee Approval:** This study was approved by the Ethics Committee of the Bakırköy Dr. Sadi Konuk Research and Education Hospital (Approval No: 2022-53).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in this study.

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