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Are Spontaneous Pneumomediastinum and Subcutaneous Emphysema Indicators of Poor Prognosis in Covid-19 Patients?

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Abstract
This study aimed to evaluate the prognostic impact of rare conditions, namely spontaneous pneumomediastinum and subcutaneous emphysema, in patients with COVID-19. A retrospective study was conducted to assess a total of 58 adult patients with COVID-19 pneumonia who developed or did not develop spontaneous pneumomediastinum and subcutaneous emphysema between March 2020 and January 2022. The presence of pneumomediastinum and subcutaneous emphysema, along with factors such as age over 70, comorbidities, and length of stay in the intensive care unit, showed a statistically significant association with increased mortality compared to patients who did not develop these conditions ($p < 0.05$). Advanced age (over 70), longer stays in the intensive care unit, presence of comorbidities, and higher mortality rates were found to hurt the prognosis of COVID-19 patients.

1. Introduction

COVID-19 was first detected in China in December 2019 and quickly spread worldwide, prompting the World Health Organisation to declare it a pandemic in March. Pneumonia is a common manifestation of COVID -19 PM was first described by Laennec in 1819. In 1939, Hammaan described possible causes of spontaneous PM (Cucinotta D, 2020, Mousa S, 2019).

Spontaneous pneumomediastinum (PMD) refers to the presence of air in the mediastinum and subcutaneous tissues without external factors such as subcutaneous emphysema (SCE), blunt trauma or mechanical ventilation. The exact mechanism of its development is not yet fully understood. However, it is thought that severe pneumonia can lead to extensive damage and rupture of the alveoli (Quincho-Lopez A , 2020).

This disease is often manifested by symptoms such as severe coughing, severe shortness of breath and chest pain (Shahsavarinia K, 2022).

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Some of the poor prognostic factors in COVID -19 patients are advanced age, male gender, smoking, concomitant diseases, elevated CRP (C-reactive protein) levels, procalcitonin levels, high neutrophil counts, low albumin levels, low platelet counts and low lymphocyte counts (Wang J, 2019).

The aim of this study is to investigate the treatment outcomes and prognosis of patients with spontaneous PMD and SCE, which are rare complications of COVID -19 pneumonia.

2. Methods

Demographic characteristics, comorbidities and smoking habits of 58 adult patients with COVID -19 pneumonia who developed spontaneous pneumothorax (Px), spontaneous PMD and SCE (n1: 27) and those who did not develop these conditions (n2: 31) were retrospectively evaluated. Patients were followed up in hospital and ICU between March 2020 and December 2022.

The study included patients who were either intubated or not intubated in the ICU and patients who were followed-up and treated in the ward. Patients who developed Px due to traumatic procedures such as central venous catheterisation and thoracentesis were excluded from the study.

Diagnosis of Px, PMD and SCE was based on physical examination, chest X-ray and/or chest CT. A chest tube was placed in patients who showed signs of Px on X-ray, except in patients who were extubated and had minimal Px. In patients with extensive PMD and SCE, transcutaneous air drainage and pre-tracheal fasciotomy were performed. In patients with moderate SCE, air was drained with a catheter in the subcutaneous area.

3. Statistical analyses

Descriptive statistical methods such as frequency, percentage, mean, standard deviation and range (min-max) were used to analyse the research data. Chi-square test ($\chi 2$) or Fisher's exact test was used to compare qualitative data. The Mann-Whitney U test was used for comparisons between groups with non-normally distributed qualitative data. The accepted level of statistical significance was set at $p < 0.05$. Data analysis was performed using the software EPI Info 7.2 (EPIINFO, CDC, Atlanta, USA).

4. Results

In our study, 31 (53.4%) of the 58 patients were female and 27 (46.6%) were male. The age range was from 23 to 84 years, with an average age of 68 years. All patients tested positive for COVID -19 by PCR. Of them, 17 (29%) required mechanical ventilation in the ICU, 3 (5%) were extubated and received oxygen therapy, and 38 (66%) continued their follow-up and treatment in hospital.

Spontaneous PMD and SCE developed in 27 (46.6%) patients (15 females (F) and 12 males (M)). Of this group, 3 (5%) patients required tube thoracostomy and closed underwater drainage due to Px. In 5 (%) of the patients, no surgical intervention was required due to minimal Px and it regressed spontaneously (Fig. 1).

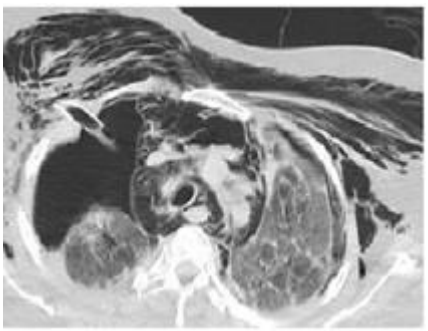

Figure 1. Shows the chest CT of a patient with SCE, spontaneous PMD and Px with a right-sided tube thoracostomy.

Among the patients, 19 (32.7%) had chronic obstructive pulmonary disease (COPD), 11 (18.9%) had diabetes mellitus, 3 (5%) had liver cirrhosis, 12 (20.6%) had hypertension, 7 (12%) had heart failure, 4 (6.8%) had renal insufficiency and 2 (3%) had malignancy as concomitant disease. In addition, 18 patients (31%) had a history of smoking.

Of the total number of patients, 51 (87.9%) recovered under medical treatment and were discharged. Morbidity was observed in 35 (60.3%) patients and 7 (12%) patients (M: 4 and F: 3) died. Of the patients who died, 6 (10.3%) had spontaneous PMD and SCE. It is worth noting that 2 of the patients who died had received a single dose of the vaccine CoronaVac (Sinovac, China) and 1 patient had a recent Covid-19 infection.

The mean age of the cases included in the study was 63.28 ± 16.09 years (median = 68). The minimum age was 23 years and the maximum age was 84 years. The mean age of cases who developed spontaneous PMD and SCE was 70.33 ± 15.05 years, which was statistically significantly higher than the mean age of those who did not develop these conditions (57.13 ± 14.56) ($p = 0.001$).

Of the cases with spontaneous PMD and SCE, 74.1% were over 70 years of age, while 65% of the cases that did not develop were under 70 years of age. This difference was statistically significant ($p = 0.000$). There was no statistically significant sex difference between those who developed spontaneous PMD and SCE and those who did not ($p = 0.829$).

Age may be considered a potential risk factor for the development of these conditions, as spontaneous PMD and SCE are more commonly observed in older age groups. However, gender was not found to be a determining factor for the development of these diseases (Fig. 2).

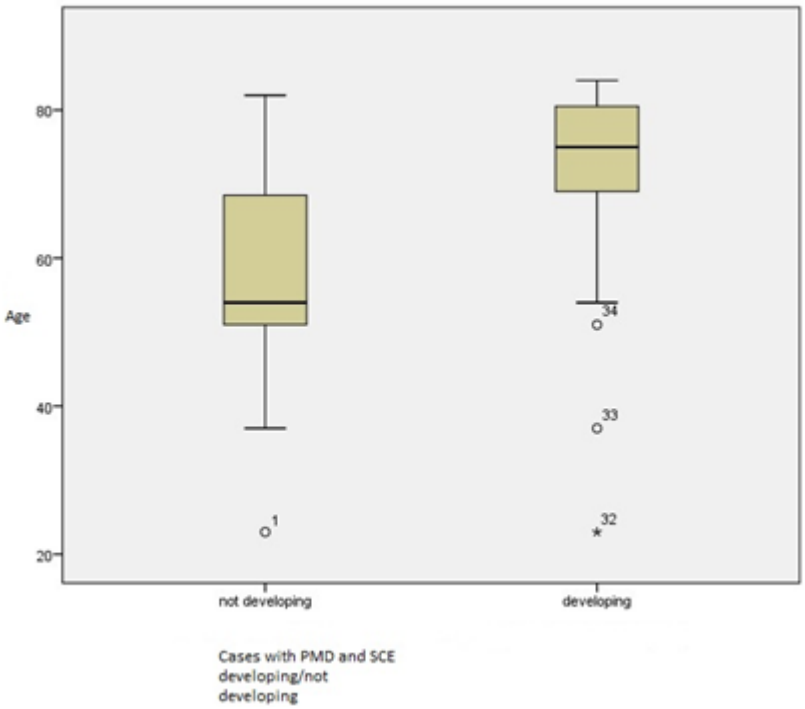

Figure 2. Age distribution of patients with and without spontaneous PMD and SCE.

It was found that the rate of development of additional diseases was statistically significantly higher in cases with spontaneous PMD and SCE than in cases without development ($p = 0.009$). This suggests that these diseases increase the risk of complications and tend to trigger or co-exist with additional health problems.

Of the patients who spontaneously developed PMD and SCE, 59.3% required admission to the ICU, while this rate was 12.9% for patients who did not spontaneously develop PMD and SCE, and the difference was statistically significant ($p = 0.000$). This suggests that patients who spontaneously develop PMD and SCE have a more severe clinical course and a higher need for intensive care.

The mortality rate for cases with spontaneous PMD and SCE was 22.2%, compared to 3.2% for non-occurring cases. This difference proved to be statistically significantly higher ($p = 0.042$). This shows that these diseases can lead to serious consequences, including death (Table 1).

Table 1. Distribution of demographic and disease-related variables in patients with and without spontaneous PMD and SCE.

		Patients without spontaneous PMD and SCE (n=31)	Patients with spontaneous PMD and SCE (n=27)	**p**
Gender	Female/Male	17/14 (%54,8/%45,2)	14/13 (%51,9/%48,1)	0,820[a]
Age	Year	57,13 ± 14,56 (median=54)	70,33 ±15,05 (median=75)	**0,001**[b]
Additional Disease	No/Yes	21/10 (%67,7/%32,3)	9/ 18 (%33,3/%66,7)	**0,009**[a]
Tracking Location	ICU/Service	4/27 (%12,9/%87,1)	16/11 (%59,3/%40,7)	**0,000** [a]
Mortality	Alive/Dead	30/1 (%96,8/%3,2)	21/6 (%77,8/%22,2)	**0,042** [c]
Old Age	<70/=>70	25/6 (%80,6/%19,4)	7/20 (%25,9/%74,1)	**0.000**

[a] : Chi-Square Test (n/%), [b] : Mann-Whitney U Test (Mean±SD), [c] : Fisher Exact Test (n/%)

5. Discussion

The causes of pneumomediastinum in COVID -19 patients are not fully understood. Spontaneous PMD in COVID -19 patients may occur as a result of diffuse alveolar injury caused by a cytokine storm or direct viral infection of type I and II pneumocytes. This can weaken the alveolar membranes, making them more susceptible to rupture and allowing air to escape into the surrounding bronchial sheaths and perivascular space. This phenomenon is known as the "Macklin phenomenon" (Zhou C, 2020).

Radiological investigations such as chest X-rays and CT play a crucial role in the diagnosis of pneumomediastinum. These imaging studies can usually detect subcutaneous emphysema. The various, albeit rare, complications of COVID -19 include Px, spontaneous PMD and SCE. There are very few reports of spontaneous PMD in COVID -19 cases. Although spontaneous PMD can cause severe respiratory and circulatory problems, it usually resolves on its own. In COVID -19 cases, PMD has been reported to occur independently of mechanical ventilation (Shan S, 2020).

The diagnoses of patients with spontaneous PMD and SCE in our study were also made by physical examination, chest X-ray and CT.

The development of spontaneous PMD and SCE in COVID -19 patients, along with additional medical problems, advanced age, gender and smoking, may worsen the prognosis. People with pre-existing conditions such as lung and heart disease, diabetes, high blood pressure, obesity and problems with the immune system are at higher risk of complications. These conditions can interfere with treatment and the recovery process. Older adults are generally more vulnerable due to a weakened immune system, the presence of concomitant diseases and general health. The exact influence of gender on the prognosis of COVID -19 patients is not yet fully understood. However, some studies suggest that men are more likely to develop and suffer more severe disease symptoms compared to women (Sun R, Sadiq Z, 2021).

In patients with COVID -19, the occurrence of spontaneous massive PMD has been reported to be more common in men. These investigators have advocated that urgent drainage of the mediastinum could be life-saving in these patients and that early diagnosis and prompt treatment could help reduce the expected high mortality (Aghajanzadeh M, 2023).

Imam et al. reported that advanced age and increasing number of comorbidities were independent predictors of in-hospital mortality in COVID -19 patients (Imam Z, 2020).

In a study conducted by Martinelli et al. it was found that the development of pneumothorax in the setting of COVID -19 increased mortality in patients with additional conditions such as diabetes mellitus, hypertension and heart failure. However, no statistically significant difference was found. Another multicentre retrospective case series involving 16 centres and a total of 71 COVID -19 patients reported that Px and PMD did not affect mortality in COVID -19 patients younger than 70 years, but significantly lower survival rates were observed in patients older than 70 years (Martinelli AW, 2020).

Another study reported that in COVID -19 patients with pneumonia without concomitant disease, the occurrence of spontaneous PMD was associated with progressively more severe pneumonia and extensive parenchymal involvement (Loffi M, 2020).

After intubation, Px and/or PMD occur more frequently in patients with COVID -19. They are often the result of alveolar rupture, air leak and intra-abdominal intrathoracic pressure. In non-intubated COVID -19 patients, subcutaneous emphysema and spontaneous PMD are rarely observed; the incidence is 3.0 and 1.2 per 100,000, respectively, but the frequency of these conditions in COVID -19 patients is unclear. So far, only a few cases have been reported. The mechanism of pneumomediastinum in non-intubated COVID -19 patients is not well understood (Zayet S, Chen N , 2020).

Al Azzawi et al. indicated in their studies that the course and treatment outcomes of COVID -19 pneumonia patients who spontaneously develop PMD and SCE are more eventful and worse than in patients who do not develop these complications. It has been suggested that this situation may worsen prognosis (Al-Azzawi M, 2020).

Hazariwala et al. and Vazzana and colleagues found that COVID -19 pneumonia impedes disease progression, but more data are needed to determine risk factors and prognostic role (Hazariwala V, Vazzana N, 2020).

Rawand et al found that oxygen therapy, bed rest, analgesics and air extraction through a supraclavicular incision are the best options for the treatment of SCE and spontaneous PMD and that further studies are needed to explain the mechanisms (Rawand AE, 2021).

In our study, there was no statistically significant difference in terms of gender between those who developed spontaneous PMD and SCE and those who did not.

We observed that individuals who developed spontaneous PMD and SCE had a higher mean age and were more often found in the older age groups. They were more susceptible to underlying diseases, required more intensive care and were consequently

associated with more severe clinical conditions. We also found a higher mortality rate in this group.

6. Conclusion

Our study shows that spontaneous PMD and SCE are rare complications observed in critically ill COVID -19 patients. Although we cannot say with certainty that the development of spontaneous PMD and SCE alone has a direct negative impact on prognosis, it is evident that prognosis is influenced by several factors, including an age of more than 70 years, a longer stay in the ICU, the presence of comorbidities and a higher mortality rate. These findings suggest that the presence of spontaneous PMD and SCE may serve as a marker for more severe disease and worse outcomes in this patient group.

Ethics

Ethical approval for this study was granted by the Ethics Committee of the University of Health Sciences, Haseki Training and Research Hospital (resolution no. 368).

Author contributions

Conception and design: TD, GC. Data collection and search: TD, GC. Drafting the article: TD, GC, FK. Final approval of the version: TD, GC, FK. All authors read and approved the final manuscript.

Conflict of interest declaration

All authors declare that they have no competing interests.

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