”VICTOR BABEȘ” UNIVERSITY
OF MEDICINE AND PHARMACY FROM TIMISOARA
FACULTY OF MEDICINE
DEPARTMENT IX SURGERY I

DRĂGHICIU ADINA MARIA

Ph.D. THESIS

SPONTANEOUS PNEUMOTHORAX AND PNEUMOMEDIASTINUM : SERIOUS COMPLICATIONS OF SARS-COV-2 INFECTION

Scientific Coordinator

PROF. Ph.D. HABIL. DR. OVIDIU ALEXANDRU MEDERLE

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INTRODUCTION

Spontaneous pneumothorax (SP) and spontaneous pneumomediastinum (SPM) have been cited as complications associated with coronavirus disease 2019 (COVID-19) pneumonia, especially in mechanically ventilated patients, secondary to barotrauma (1). However, several studies and isolated cases of SP and SPM have been published with patients who have not been previously mechanically ventilated, or who have not undergone potentially risky interventions, such as thoracentesis or central venous catheter insertion (2).

The incidence of SP or SPM in patients with severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection is currently unknown. Current data show an incidence ranging from 1 ‰ in non-ventilated patients (2) to 12.8–23.8% (3) for those who were mechanically ventilated.

The current literature is also controversial regarding the potential risk factors for developing SP or SPM in non-ventilated COVID-19 patients, but the outcome was certainly worse for this association in most of the studies (1, 4).

Healthcare professionals need to pay close attention to the "red flags" in more difficult conditions, when assisting a patient with dyspnea and chest pain during the pandemic, in order to follow appropriate therapy strategies, when full protective equipment makes it difficult to examine these patients.

GENERAL PART

1. CORONAVIRUS DISEASE

Severe Acute Respiratory Syndrome Coronavirus 2, the virus responsible for COVID-19 disease, belongs to the family *Coronaviridae* of the order *Nidovirales,* subfamily *Coronavirinae* (5). The suspicion of SARS-CoV-2 infection is primarily based on epidemiological history, typical clinical manifestations, imaging abnormalities observed in chest computed tomography (chest-CT) like ground-glass opacities and laboratory tests, including lymphopenia, elevated lactate dehydrogenase and D-dimer (6). The diagnosis of COVID-19 is confirmed by detection of SARS-CoV-2 RNA by reverse-transcription polymerase chain reaction (RT-PCR) from nasal and oropharyngeal swabs (7).

Mortality in COVID-19 disease was primarily associated with clinical complications, especially in elderly, patients with chronic diseases and pregnant woman, which are more likely to evolve to severe forms, often requiring mechanical ventilation, intensive care admission and antibiotic treatment for secondary infections (6). Several reports showed that the presence of comorbidities like hypertension, diabetes mellitus, cancer, cardiovascular disease, chronic kidney disease, vitamin deficiency and oxidative stress, is associated with a greater severity of SARS-CoV-2 infection (8). COVID-19 patients with comorbidities are more likely to develop coagulopathies due to prolonged immobilization and inflammatory status, especially the ones admitted in ICU (9). Several risk factors were conected with in-hospital mortality, such as hypoxia, systemic inflammatory response, and the risk associated with hospitalization (10).

Most of the patients with SARS-CoV-2 infection develop mild symptoms like cold and flu but some of them will experience severe symptoms leading to acute respiratory distress syndrome (ARDS), cytokine release syndrome, multiple organs and systems failure, septic complications or venous thromboembolism (10).

The most frequent features of COVID-19 infections are respiratory ones. In the more severe forms of the disease, patient's clinical condition is aggravated by viral pneumonia which can evolve to hypoxic respiratory failure, the most common cause of death (11). A variety of complications were described for patients who needed ICU admission, like over imposed pneumonia, thrombotic complications like pulmonary embolism or venous thromboembolism, but also barotrauma like pneumothorax and pneumomediastinum (12).

2. SPONTANEOUS PNEUMOTHORAX AND PNEUMOMEDIASTINUM

Annual incidence of primary spontaneous pneumothorax described in literature is between 15.5 and 22.7 per 100,000 individuals with a female:male ratio of 1:3.3 and 1:5; the reoccurrence risk of 25% to 54% is influenced by the presence of a chronic pulmonary condition (13). Regarding the SSP, the incidence for male gender is 6.3 per 100,000 patients, three times higher than in women, where it is 2 per 100,000 patients (14). The incidence for spontaneous pneumomediastinum is one case per 10,000 patients admitted to hospital (14).

Spontaneous pneumothorax or pneumomediastinum diagnosis is based on the clinical suspicion, history and is confirmed by imaging investigation. Arterial gas usually shows hypoxemia, sometimes associated with a mild hypercapnia especially for patients with secondary spontaneous pneumothorax. (15).

The most readily available investigation in emergency department (ED) is bedside pulmonary ultrasonography (13). This investigation can be used even for the most critically ill patients to confirm SP. In one study run by Garofalo et al (13), pulmonary ultrasonography had a diagnosis efficacy for spontaneous pneumothorax of 98.91% with 95.65% sensibility and 100% specificity when it was compared with chest X-ray or chest-CT.

Another diagnostic method, highly used over the years, is the standard postero-anterior chest x-ray in the erect position (PA chest x-ray). It is a cheap, accessible investigation, but it has certain limitations like accurate quantification of the size of pneumothorax (15).

Chest-CT represents the golden standard for the diagnosis of SP, pneumomediastinum, surgical emphysema, and some of the chronic pulmonary conditions, especially if there is uncertainty regarding X-ray interpretation. Also, chest-CT allows accurate sizing of the pneumothorax from the lung line to the parietal pleura at the hill level (15).

ED management of SP depends on several factors. The main objective is to recognize and urgently treat tension pneumothorax. Administration of additional oxygen via reservoir mask with 100% concentrations, is a simple and quick maneuver, which brings a benefit to patients with SP, firstly due to the decrease of respiratory effort, and secondly due to the increase of the air absorption rate from the pleural space four times faster, compared to patients who do not receive additional oxygen (16).

If the patient is hemodynamically unstable and shows clinical signs of a tension pneumothorax, such as unilateral lack of chest expansion, unilateral absence of breathing sounds, deviated trachea to the opposite side, surgical emphysema, distend jugular veins, pale and sweaty skin, prolonged capillary refill time, hypotension, tachycardia, and when available, specific ultrasound signs of pneumothorax, initial maneuver is needle decompression on the 2nd intercostal space on the mid clavicular line, followed as soon as possible by thoracostomy with thoracic drain placement in the 4th or 5th intercostal space on the mid axillary line (16, 17).

SPM has been associated with a favorable outcome (18, 19) especially if chest-CT is available to exclude nonspontaneous PM. In most of the cases, conservative treatment is the only management in case of SPM (20).

3. SPONTANEOUS PNEUMOTHORAX ASSOCIATED WITH SARS-COV-2 INFECTION

Since the beginning of the pandemic, isolated cases of pneumothorax have been reported in patients with SARS-CoV-2 infection, more often for patients with severe forms of the disease who received noninvasive or invasive mechanical ventilation.

The incidence of SP or SPM in patients with COVID-19, the respiratory disease caused by SARS-CoV-2, is currently unknown (1). A large study by Miró et al. (2) reported a small number of patients with SP and COVID-19, with an incidence of less than 1‰. A systematic review recently published by Chong et al. (3) highlighted a low incidence of pneumothorax in hospitalized COVID-19 patients (0.3%), but that increased to 12.8–23.8% for those who were mechanically ventilated.

Since the first cases reported at the beginning of the pandemic, a number of factors have been incriminated in the occurrence of SP in patients with SARS-CoV-2 infection. The most common factor was mechanical ventilation, as the occurrence of SP in mechanically ventilated patients was more frequently reported in positive COVID-19 patients, compared to other causes of ARDS or viral pneumonia (21). Another reason discussed as a risk factor in SP, was the increased respiratory effort in patients with COVID-19 pneumonia that may induce Self-Inflicted Lung Injury (PSILI)(22).

Considering that SP or SPM associated with SARS-CoV-2 infection was also reported in patients who were not mechanically ventilated before diagnosis, other factors related to viral impregnation were also blamed. Increased susceptibility to lung injury, including also the SP risk could be associated with the damage of ACE2 and increased values of the inflammatory markers (CRP, ferritin, inflammatory interleukins such as IL-6, tumor necrosis factor) (21).

The prognosis of COVID-19 patients may be negatively influenced if they develop complications such as SP or SPM. Konx et al reported in a recent study a higher 30-day mortality and a higher incidence of SPM in patients with ARDS and COVID-19 who developed PS, compared to non-COVID patients with ARDS from the pre-pandemic period (23).

RESEARCH

1. CLINICAL TRIAL

We conducted a one-year review of the medical records in the emergency departments of two tertiary hospitals: Emergency Clinical Municipal Hospital and "Pius Brinzeu" Emergency Clinical County Hospital, both teaching hospitals affiliated with Victor Babes University of Medicine and Pharmacy in Timisoara.

The aim of our retrospective research was twofold:

(a) to investigate the characteristics of patients with SP-SPM (both with and without COVID-19) and compare them to patients with sole COVID-19;

(b) to quantify the risk of in-hospital mortality associated with SP-SPM and COVID-19.

MATERIALS

The study design followed a retrospective case–control protocol: a review was carried out on 64,845 electronic medical records (EMRs) of patients admitted to the two EDs between 1st April 2020 and 31st March 2021. Seventy cases of SP-SPM were identified according to study protocol in the hospitals' computer systems through keywords-based automatic search. The results were then manually double-checked for compliance with the inclusion criteria and completeness of the essential required EMR data. They comprised the case group.

For each case, two controls were included from consecutive patients admitted with SARS-CoV-2 infection at the same ED, immediately before (one) and after (one) the case patient. In the situation of two or more consecutive cases, the allocation was adjusted accordingly, keeping the same ratio of 2:1 between controls and cases.

Starting in March 2020, the hospital admittance protocols required all patients to undergo chest-imaging (either X-ray or computed tomography) and a reverse transcription–polymerase chain reaction (RT–PCR) test for SARS-CoV-2 infection, irrespective of symptoms or diagnosis.

The case group had the following inclusion criteria:

- aged 18 or older;
- presence of pneumothorax or pneumomediastinum on chest radiography or computed tomography (CT);
- RT-PCR test performed for SARS-CoV-2 infection.

The exclusion criteria were as follows:

- aged below 18 years;
- post-traumatic pneumothorax or pneumomediastinum;
- invasive or non-invasive mechanical ventilation initiated before arrival at the ED or before the diagnosis;
- post-procedural pneumothorax or pneumomediastinum, such as thoracocentesis, or a central venous catheter in the jugular or subclavian veins.

Inclusion criteria for **the control group** were as follows:

- aged 18 or older;
- RT-PCR confirmation of SARS-CoV-2 infection in a nasopharyngeal swab.

Age below 18 years was the only exclusion criterion for the control group.

Within the control patients, some EMR data could not be retrieved for all the variables. There were two reasons for the missing values in the hospital information systems:

- at the beginning of the pandemic, there was not a clear protocol for COVID-19 patients, so medical investigation was dependent on the doctor in charge;
- at certain times, the flow of patients in the ED overwhelmed the hospital's laboratory capacity or the availability of reactants for all the requested blood tests.

Since the priority for data retrieval was to comply with the need to avoid any possible bias, the choice was made to keep the incomplete records in the working data set if the missing laboratory results were not essential to the study objectives. No data imputation was performed.

The primary outcome of our study was in-hospital mortality, a health indicator that captures the severity of the medical condition and the healthcare services' capacity of response (24, 25). In-hospital death was defined as a medical encounter with discharge status of "died" or "died in a medical facility".

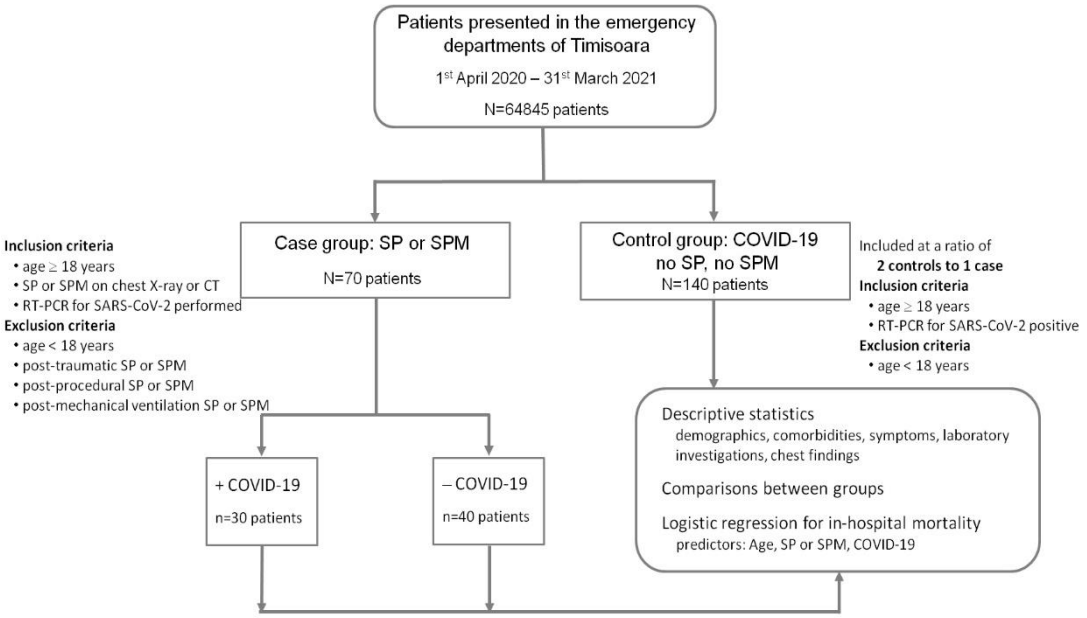

Figure 1. Study design

METHODS

We collected data regarding: demographics, comorbidities, symptoms, vital signs on arrival at the ED (temperature, blood pressure, SpO2), days passed from the onset of pneumothorax symptoms to presentation in the ED, laboratory tests, radiological findings on chest radiography and CT imaging, extension of pneumothorax, extension of ground glass opacities, treatment options for SP-SPM patients, use of steroid and antiretroviral treatment, other information related to the length of hospitalization, need for oxygen therapy, need for ICU admission, need for mechanical ventilation during the hospitalization, and final outcome.

Descriptive statistics included the observed frequency counts (percentage) for categorical variables and median (Inter Quartile Range) or mean (min and max) for numerical variables. Mean and standard deviation for numerical variables were also included, regardless of distribution. Univariate non-parametric statistical tests were applied to compare the distribution of data across two or multiple groups, as appropriate (either Mann–Whitney U/T-test or Kruskal–Wallis/ANOVA tests, respectively).

The Chi-square statistical test (either asymptotic or Monte Carlo simulation with 10,000 samples) was applied to check the statistical significance of the association between the categorical

variables. The Shapiro–Wilk statistical test was employed to test for normality (all the numerical variables had non-normal distributions).

A step-wise logistic regression model was applied with mortality as the outcome, and age, a positive diagnosis of SP-SPM or COVID-19 as possible independent predictors (controlling for gender and smoking status), based on the research hypothesis and the preliminary univariate analysis. The Akaike information criterion (AIC) was used to select the best fitting model when applying the logistic regression.

We conducted a post hoc sensitivity analysis, comprising:

(a) a post hoc power analysis for the logistic regression model;

(b) analysis of alternative regression models, employing different building strategies (26).

For the power analysis, two approaches were considered:

(a1) simple logistic regression based on observed proportions of the outcome in different groups; (27)

(a2) multiple logistic regression with binary and continuous predictors (28).

The statistical analysis was conducted at a 95% level of confidence and 5% level of statistical significance. All reported probability values were two-tailed.

RESULTS

Within the group of cases (70 patients), 30 were positive and 40 were negative for SARS-CoV-2 infection. The mean age for the SP-SPM-COVID-19 group was 48.93 ± 17.38 years, while for the SP-SPM+COVID-19 group was 64.43 ± 12.24 years.

SP-SPM+COVID-19 patients were frequently associated with hypertension, male gender, non-smoking status and older age. The most frequent symptom in SP-SPM cases was dyspnea. Although they were also present in patients within the sole-COVID-19 group, chest pain was more commonly associated with the presence of SP-SPM (43.3% in COVID-19 positive and 60% in COVID-19 negative patients versus 3.6% in the control group, $p<0.001$).

Low oxygen saturations have been associated with prolonged hospitalization, especially in patients with SP-SPM and COVID-19, in whom the average number of days of hospitalization was 21.73 ± 24.81, compared with SP-SPM patients without SARS-CoV-2 infection (10.68 ± 7.64) and those in the control group (13.14 ± 7.45). The highest mortality and need for ICU admission were observed in SP-SPM cases with associated SARS-CoV-2 infection.

The location of pneumothorax was in most of the cases unilateral and right-sided (54.3% of cases), both in positive and negative COVID-19 patients. Subcutaneous emphysema and pneumomediastinum occurred more frequently in positive COVID-19 patients with SP compared to negative ones (43.3% versus 7.5% for subcutaneous emphysema and 53.3% versus 10% for pneumomediastinum) ($p<0.001$).

Table 1. shows the results of the regression analysis with in-hospital mortality as the outcome. A step-wise analysis was conducted, based on the Akaike information criterion (AIC): only variables that remained in the model are shown.

In all three models, the regression coefficient of age remained constant and highly significant: each additional year added a mortality risk of 9.4%; the 95% CI for OR in Model 2 was (1.054–1.135).

Based on Model 2, the SP-SPM increases almost four times the risk of death, ie at a ratio of 3.758 while controlling for the other factors in the model. Similarly, for patients of the same age, gender, smoking habit, and SP-SPM condition, the presence of COVID-19 increases the in-hospital mortality risk more than four times, ie at an OR of 4.412.

Table 1. The logistic regression model for in-hospital mortality. Models 0, 1, and 2 were built applying a step-wise logistic regression and employing AIC for model selection.

Model 0: Deceased ~ Age + GenderM + ActiveSmoker				
	Predictor	B ± Std. err	p-value	Exp (B) (95% CI)
	Age	0.091 ± 0.018	< 0.001**	1.096 (1.057 – 1.136)
	GenderM	0.206 ± 0.39	0.597	NA
	ActiveSmoker	0.057 ± 0.456	0.901	NA
	AIC_0 = 182.23, 4 df; Nagelkerke R-square = 0.279			
Model 1: Deceased ~ Age + SP or SPM Controlling for: GenderM + ActiveSmoker				
	Predictor	B ± Std. err	p-value	Exp (B) (95% CI)
	Age	0.091 ± 0.018	< 0.001**	1.096 (1.057 – 1.136)
	SP or SPM	0.761 ± 0.412	0.064#	2.14 (0.955 – 4.795)
	AIC_1 = 180.81, 5 df; (AIC_1, AIC_0), p=0.064#; Nagelkerke R-square = 0.299			
Model 2: Deceased ~ Age + SP or SPM + COVID-19 Controlling for: GenderM + ActiveSmoker				
	Predictor	B ± Std. err	p-value	Exp (B) (95% CI)
	Age	0.090 ± 0.019	< 0.001**	1.094 (1.054 – 1.135)
	SP or SPM	1.324 ± 0.489	0.007**	3.758 (1.443 – 9.792)
	COVID-19	1.484 ± 0.728	0.041*	4.412 (1.060 – 18.370)
	AIC_2 = 178.26, 6 df; (AIC_2, AIC_1), p=0.033*; Nagelkerke R-square = 0.326			

We built alternative regression models by: (1) employing the Bayesian information criterion (instead of AIC) for model selection; (2) controlling for additional possible confounders. The results were similar to those of the primary analysis.

Compared to Model 2 in the primary analysis, it includes seven comorbidities as additional independent variables. The risk associated with COVID-19 turned out to be higher, with an even larger 95% CI. The alternative regression models would also suggest a significant risk associated with asthma, but not with the other comorbidities. Based on AIC and the analysis of alternative regression models, Model 2 remained robust and reliable.

DISCUSSION

Underlying pulmonary diseases may frequently cause SP and SPM (29, 30). In our study, only small percentages of patients were admitted to the EDs with these conditions. This might suggest that SARS-CoV-2 infection alone was a major predisposing factor for SP-SPM development,

In our study, SP-SPM+COVID-19 patients were frequently associated with hypertension, male gender, non-smoking status and older age, which was consistent with the medical literature data from pre-pandemic studies (29), but also in studies which included SARS-CoV-2 patients (2, 31, 32).

Cigarette smoking is another acknowledged risk factor for developing SP-SPM (29, 30). In our study, 65% of the SP-SPM-COVID-19 were active smokers compared to 20% in SP-SPM+COVID-19 group, suggesting that smoking was a non-contributory individual risk factor for SP-SPM complications in patients with SARS-CoV-2 infection.

High blood pressure (HBP) was by far the most common comorbidity found in all patients. Comparing HBP frequency in the three groups, it seemed to be associated with SARS-CoV-2 infection, rather than SP-SPM condition.

In an observational cohort study by Qu et al, dyspnea was found to be a marker for critical forms of COVID-19. An association among chest distress, dyspnea, and shortness of breath was related to

increased mortality (33). In our research, dyspnea was the most common symptom associated with SP-SPM (93.3%). Chest pain was found to be the most specific symptom in the SP-SPM case group, regardless of COVID-19 condition. Therefore, chest pain in patients with SARS-CoV-2 infection would indicate a possible SP-SPM complication.

The peripheral oxygen saturation in room air at hospital admittance corroborated our findings on prolonged hospitalization, higher percentage of ICU admission, and higher mortality: SpO2 had the lowest values among the cases associated with COVID-19 (SP-SPM with COVID-19), who also had the most dramatic rate of death (almost 47%). Low SpO2 is acknowledged as a consequence of SARS-CoV-2 induced pulmonary infiltration.

In our study the chest CT was the most common imaging method used for SP-SPM diagnosis in the ED. Among the SP-SPM cases associated with SARS-CoV-2 infection, only 30% had extended pneumothorax (ie over 50% of the lung fields), while 50% had extended ground-glass lesions. Increased mortality in this group could have been associated with the spread of ground-glass lesions, rather than the size of pneumothorax. This finding was consistent with other published data (2, 3, 31).

The location of pneumothorax was unilateral and predominantly right-sided, regardless of COVID-19 status as seen in other published studies (2). Pneumomediastinum and subcutaneous emphysema were found in a higher proportion of patients with associated SARS-CoV-2 infection.

Hospitalization and need for ICU admission were significantly longer for SP-SPM cases with COVID-19. Even more dramatically, the proportion of deceased people in the same group was more than double that of the COVID-19 controls.

The logistic regression found a risk of death almost four times higher for SP-SPM cases compared to individuals of the same age, gender, smoking status, and SARS-CoV-2 infection. COVID-19 pneumonia brought a significant mortality risk of more than four times higher. In the regression model of mortality, age was also a significant predictor, each additional year contributing with 9.4% increase in the risk of in-hospital death. Our results were consistent with the current medical literature, in which SP related to COVID-19 pneumonia is associated with prolonged hospitalization, increased admission in ICU, and higher level of mortality (2, 3, 34, 35).

Taking all of the above into consideration, the association of SP-SPM with COVID-19 might still be under-reported. Its prevalence, risk factors, and final outcome remain unclear (34-43). Our research contributes to understanding the combination of SP, SPM and COVID-19 in non-ventilated patients, and quantifying their associated risks for in-hospital mortality.

4. CASE PRESENTATION: MASSIVE SPONTANEOUS PNEUMOTHORAX – A RARE FORM OF PRESENTATION FOR SEVERE COVID-19 PNEUMONIA

INTRODUCTION

Massive spontaneous pneumothorax may be the presentation of a patient with COVID-19 pneumonia, in which the diagnosis delay can have serious consequences, that can lead to the immediate death of the patient. The introduction of SP as a complication of SARS-CoV-2 infection can increase the responsiveness of frontline health care workers when dealing with COVID-19 patients.

Here, we describe a case of a 57-year-old woman, who had no prior lung injury or other risk factors for spontaneous pneumothorax, was never a smoker, and was not mechanically ventilated, who developed massive spontaneous pneumothorax after only 3 days of symptoms of SARS-CoV-2 infection.

CASE PRESENTATION

A 57-years-old woman with a history of essential hypertension was brought into the emergency department with acute respiratory failure, SpO_2 of 43%, that increased to 86% after oxygen delivery (through a reservoir mask).

On physical examination the patient presented tachypnea (34 breaths per minute), pale and sweaty skin, hemodynamically stable, blood pressure 127/66 mmHg, a heart rate of 109 beats/min, a body temperature of 37.8 °C, Glasgow Coma Score (GCS) = 15/15. The patient complained of fever, dry cough, dyspnea on exertion and fatigue, that started 3 days before the presentation, claiming that, during the previous night, the dyspnea suddenly worsened and an anterior chest pain appeared. She had no other comorbidities except essential hypertension under treatment.

Based on the history and clinical examination, SARS-CoV-2 infection was suspected. Prone position was initiated in order to improve ventilation, which the patient did not tolerate. She received fluids, dexamethasone and antipyretics. Blood was taken for lab tests and the pharyngeal and nasal swabs for the RT-PCR test, which came positive after several hours.

The thoracic CT scan showed massive right pneumothorax (90 mm), lung partially collapsed, slightly left-displaced heart, multiple bilateral lung infiltrates with a ground-glass aspect that occupied about 65% of lung fields—CO-RADS classification 5. The thoracostomy was performed and the chest tube was placed in the right fifth intercostal space, on the medium axillary line, under local anesthesia. The patient's condition partially improved and oxygen saturation increased after the chest tube was placed, and then she was admitted to the thoracic surgery ward.

During the day, the patient's breathing worsened, so she was transferred to the intensive care unit. Non-invasive ventilation was initiated for a few hours, but then the condition of the patient worsened again, and the endotracheal intubation and invasive mechanical ventilation were decided.

During hospitalization in the intensive care unit, the patient had a fluctuating evolution, and despite the treatment (medication, kinetotherapy, prone position, hydro-electrolyte rebalance solutions), the patient's condition was deteriorating and after19 days after admission she died.

DISCUSSION

Massive pneumothorax is a major, life-threatening emergency that must be identified and treated very promptly (44). Our patient had a massive pneumothorax that was timely solved, but still she had a fatal outcome. However, we cannot state that the size of the pneumothorax had a defining role in the patient's evolution as there are studies with COVID-19 patients experiencing small pneumothorax and still a poor prognosis (45, 46). We suspect that our patient developed SSP because of lung lesions caused by COVID-19 infection, given the fact that she was not a smoker and not known to have other risk factors.

Despite the timely diagnosis and treatment of SSP, the patient's evolution was marked by severe lung damage from COVID-19 pneumonia, and after a long hospitalization in the intensive care unit, the patient died, emphasizing the importance of the underlying lung disease in spontaneous secondary pneumothorax. Patients with COVID-19 pneumonia and SP should be carefully monitored to prevent respiratory deterioration, no matter the size of the pneumothorax (46).

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

- SP should always be considered as a differential diagnosis in the assessment of COVID-19 patients with and acute respiratory failure
- SARS-CoV-2 infection alone was a major predisposing factor for SP-SPM development in our study, due to low percentage of patients having predisposing conditions for SP or SPM development
- Cigarette smoking was not an individual risk factor for SP-SPM complications in patients with SARS-CoV-2 infection
- High blood pressure was by far the most common comorbidity found in all patients and it seemed to be associated with SARS-CoV-2 infection, rather than SP-SPM condition
- The peripheral oxygen saturation in room air at hospital admittance corroborated our findings on prolonged hospitalization, higher percentage of ICU admission, and higher mortality in SP-SPM COVID-19 positive patients
- Chest pain and dyspnea in patients with SARS-CoV-2 infection requires an urgent investigation to rule out SP–SPM
- Cough, a frequent symptom in our study in positive COVID-19 patients can be the trigger of a spontaneous pneumothorax or pneumomediastinum, therefore in these patients it can represent a „red flag"
- Pneumomediastinum and subcutaneous emphysema was found in a higher proportion of patients with associated SARS-CoV-2 infection
- The evolution of patients with SP or SPM and the increased mortality cannot be attributed to the size of the pneumothorax, but rather to the expansion of the groundglass lesions
- SP–SPM is a serious complication of SARS-CoV-2 infection that increases the risk of in-hospital mortality by almost four times
- Its association with COVID-19 pneumonia led to prolonged hospitalization and a high risk of fatal outcomes, especially among the elderly

The post hoc sensitivity analysis supports the robustness of our results. The consistency between the primary logistic regression and the sensitivity analysis confirmed our findings' credibility.

The association of SP-SPM with COVID-19 might still be under-reported. Its prevalence, risk factors, and final outcome remain unclear. Our research contributes to understanding the combination of SP, SPM and COVID-19 in non-ventilated patients, and quantifying their associated risks for in-hospital mortality. Knowing these risk factors and warning signs in a patient with SARS-CoV-2 infection is a huge benefit for front-line medical personnel, who can suspect earlier the presence of a pneumothorax or pneumomediastinum and treat it in a timely manner, in order to prevent clinical deterioration.

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