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A Single-Center Experience on the Treatment Outcomes of Patients with COVID-19-Pleural Disorders: Lessons for the Future

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ABSTRACT

Background: Pleural disorders in novel coronavirus disease 2019 (COVID-19), responsible for the deaths of more than 6.7 million people worldwide, are relatively uncommon and underappreciated findings. The severity of the pleural disease in these patients correlates with the treatment outcome and overall prognosis. **Objective:** We aim to review our experience with treatment modalities and prognosis in 45 patients with COVID-19, who were treated at our Clinic between April 2020 and October 2021. **Methods:** We conducted a retrospective, single-center, cross-sectional study. Demographic data, the type of thoracoscopic intervention(s), and treatment outcome for 45 patients included in this study were recorded for every patient. We analyzed the type and number of treatment modalities according to the pleural disorder, and the outcome of the treatment. **Results:** Pneumothorax was the most common COVID-19-related pleural disorder, followed by the pleural effusion. Tube thoracostomy was the mainstay of treatment, performed in 84.4% of patients with unilateral pleural complications. In total, 20% of our patients were on mechanical ventilation, and all of them had a fatal outcome. We found statistical significance in comparison to the percentage of fatal outcomes between patients treated with and without mechanical ventilation ($p=0.000$). **Conclusion:** COVID-19-related pleural disorders are prognostic markers of disease progression. Mechanically ventilated patients who require tube thoracostomy have an unfavorable prognosis.

Keywords: pleural effusion, COVID-19, pneumothorax, thoracocentesis, chest tube.

1. BACKGROUND

As of the end of January 2023, severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2), caused by a member of the *Coronaviridae* family, has taken more than 6.8 million lives worldwide (1). Acute lung injury in the form of endothelialitis, which promotes alveolar edema, and microangiopathy are the hallmarks of pulmonary vascular endothelium disorder. Intensive care unit (ICU) patients with severe SARS-CoV-2 may exhibit various respiratory symptoms, which in some cases lead to the development of pneumonia and acute respiratory distress syndrome (ARDS).

The scope of pleural disorders in patients with coronavirus disease 2019 (COVID-19) is still not well documented and therefore underappreciated. Two prominent pleural abnormalities, pleural effusion and pneumothorax, are considered late features of disease progression (2).

Even though pleural disorders occur in a minority of patients with COVID-19, i.e. the incidence of pleural effusion was 7.3% among the 47 observational studies (3), whereas pneumothorax occurred in only up to 1% of patients (4), they may be associated with disease severity and overall prognosis. Certain factors, such as gender, age, or pre-existing comorbidities can influence the disease course and treatment outcome; nevertheless, COVID-19 pneumonia not responding to non-invasive respiratory support will eventually require mechanical ventilation.

We wanted to summarize the most frequent pleural disorders related to the COVID-19 infection as well as to share our experience with thoracoscopic treatment and the outcome of the disease.

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2. OBJECTIVE

This study aimed to analyze effects of various treatment modalities and prognosis in 45 patients with COVID-19-related pleural disorders, who were treated at our Clinic between April 2020 and October 2021.

3. PATIENTS AND METHODS

Patients

In this retrospective, cross-sectional study, we collected data from 45 patients admitted to the Clinical Center University of Sarajevo between April 2020 and October 2021 with COVID-19 infection and at least one pleural complication that required a thoracoscopic intervention. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assays of specimens collected by a nasopharyngeal swab were used to confirm COVID-19. Radiologically verified accumulation of air (pneumothorax), fluid (pleural effusion), as well as other less common pleural disorders, i.e. pneumomediastinum, and other related conditions (such as subcutaneous emphysema), were documented for each patient, as well as the treatment modality and prognosis.

Methods

We recorded demographic data (gender and age group), radiological finding(s) (pleural disorder(s)), and thoracoscopic intervention(s) (one or more pleural taps, tube thoracostomies, and incisions for emphysema) for every included patient. Patients who had a positive RT-PCR assay for COVID-19 with related pleural complications, which required single or multiple thoracoscopic interventions, were included in the study. Patients with negative RT-PCR assay with the pleural disorder(s) and patients with the so-called post-acute COVID-19 syndrome with pleural complications, were excluded from the study. Patient data were obtained using the available medical history and were anonymized according to the Regulation on the protection of personal data.

Statistical analysis

Descriptive and inferential statistical analyses were applied. Categorical variables were expressed as counts and percentages. Continuous variable with normally distributed data was presented as means and standard deviation and continuous variable with non-normally distributed data was presented with median and interquartile range (IQR) values. *Independent t-tests* were performed to compare the mean of continuous variables with normally distributed data, and *the Mann-Whitney test* was applied to compare the distribution of non-normally distributed data. *The χ^2 test* was applied to compare the proportion of categorical variables. Statistical analysis was performed by using the *SPSS software package version 20.0*. A p-value less than 0.05 ($p < 0.005$) was considered statistically significant.

4. RESULTS

Between April 2020 and October 2021, a total of 4520 patients with positive RT-PCR assay for COVID-19 were admitted to the Clinical Center University of Sarajevo. Among them, 45 patients (1%) had at least one

COVID-19-related pleural disorder and were therefore enrolled in our study.

Overall, there were 28 (62.8%) male and 17 (37.2%) female patients. The most common COVID-19-related pleural disorder was pneumothorax (reported in 21 (46.7%) patients), followed by pleural effusion in 19 (42.2%) patients, and other complications that required a thoracoscopic intervention, i.e. subcutaneous emphysema and, etc. in five (11.1%) patients. More than half of 19 patients with pleural effusion and three-fifths of 21 patients with other pleural complications, 12 (63.0%) and 4 (80.0%), respectively, were over 60 years old, while almost half of the patients with pneumothorax, i.e. 10 (48.0%) patients, were in the age group 31-60 years. The median (IQR) age of all observed patients was 61 (49 to 72) years.

Tube thoracostomy was the gold standard in the treatment of patients with COVID-19-related pleural disease(s). A thoracostomy tube is placed between the mid- to the anterior axillary line in the fourth or fifth intercostal space above the rib in order not to injure the intercostal bundle (artery, vein, nerve), and the procedure itself is performed with local anesthesia. It was performed in 38 (84.4%) patients with unilateral pleural complications, whereas in five (11.1%) patients, chest tubes needed to be placed bilaterally. On the other hand, thoracentesis was performed in eight (17.8%) patients and pectoral incisions in four (8.9%) patients with extensive subcutaneous emphysema. Thoracentesis was performed in either an upright (sitting) position, in a recumbent, or even a supine position (in ventilated patients). We performed either a unilateral or bilateral infraclavicular/pectoral incision(s) in patients with subcutaneous emphysema (depending on the severity and extent of the emphysema).

In severe cases, COVID-19-pneumonia-related acute respiratory failure not responding to non-invasive respiratory support requires mechanical ventilation. Even though mechanical ventilation can be a life-saving therapy, it can put patients in even greater danger of lung injury if airway pressure and flow are not tailored to the respiratory system mechanics of the ventilated patient. Out of total 45 patients with COVID-19-related pleural disease, 11 (20%) were on mechanical ventilation. Nine patients with COVID-19-related pneumothorax, one patient with COVID-19-related pleural effusion, and one patient with other COVID-19-related pleural disorders were intubated and placed on mechanical ventilation.

The mean (SD) of time from onset of symptoms to intubation in patients with COVID-19-related pleural disorder(s) was 3.00 ± 0.00 in patients with pleural effusion, 13.44 ± 11.38 in those with pneumothorax and 27.00 ± 0.00 days in patients with other conditions, respectively. The mean (SD) of onset of symptoms to intubation of all 11 patients on mechanical ventilation was 13.73 ± 11.53 days. We performed one or more interventions in 9 of 11 patients on mechanical ventilation. Seven patients (64%) were men. Out of the total of 11 patients on mechanical ventilation, eight (73%) were over 60 years old. The

COVID-19 related pleural disorder		Pleural effusion		^a Pneumothorax		^b Other		Total	
Variable		N	%	N	%	N	%	%	N
Intubation from onset of symptoms (days)		3.00±0.00		13.44±11.38		27.00±0.00		13.73±11.53	
Thoracosurgical intervention	Yes	0	0.0	8	88.9	1	100.0	9	81.8
	No	1	100.0	1	11.1	0	0.0	2	18.2
Gender	Female	1	100.0	2	22.2	1	100.0	4	36.4
	Male	0	0.0	7	77.8	0	0.0	7	63.6
Age group	≤30	0	0.0	0	0.0	0	0.0	0	0.0
	31-60	1	100.0	2	22.2	0	0.0	3	27.3
	>60	0	0.0	7	77.8	1	100.0	8	72.7
Age	Me (IQR)	39.00		70.67±13.31		61.0		66.91±15.36	

Table 1. Characteristics and thoracosurgical intervention(s) depending on COVID-19 pleural disorder(s) in patients on mechanical ventilation (n=11). ^p Pneumothorax and pneumothorax with either subcutaneous emphysema, pleural effusion, pneumomediastinum, cystic lungs, pleural empyema, and/or serial rib fracture; ^b Other include the following diagnosis: other cases of hydrothorax, exudative pleuritis;

Outcome		Died (n=18)		Recovered (n=27)		P value	Total (n=45)	
Variable		n	%	n	%		n	%
Gender	Female	8	47.1	9	52.9	^c 0.451	17	37.8
	Male	10	35.7	18	64.3		28	62.7
Age group	<30	0	0.0	3	100.0	-	3	6.7
	31-60	4	23.5	13	76.5		17	37.8
	≥60	14	56.0	11	44.0		25	55.6
Age	/Me(IQR)	67.3±12.3		54.52±20.49		^d 0.022*	61(49-72)	
Pleural complication	Pleural effusion	5	26.3	14	73.7	-	19	42.27
	^a Pneumothorax	12	57.1	9	42.9		21	46.7
	^b Other	1	20.0	4	80.0		5	11.1
Location	Right	9	45.0	11	55.0	^c 0.270	20	44.4
	Left	4	25.0	12	75.0		16	35.6
	Bilateral	5	55.6	4	44.4		9	20.0
Number of pleural complications	1	13	36.1	23	63.9	-	36	80.0
	2	3	42.9	4	57.1		7	15.6
	3	2	10.0	0	100.0		2	4.4
Mechanical ventilation	Yes	11	100.0	0	0.0	^c 0.000*	11	24.4
	No	7	20.6	27	79.4		34	75.6

Table 2. Outcome of treatment in SARS-CoV-2 patients with pneumothorax, pleural effusion and other pleural complications (n=45). ^p Pneumothorax and pneumothorax with either subcutaneous emphysema, pleural effusion, pneumomediastinum, cystic lungs, pleural empyema, and/or serial rib fracture; ^b Other include the following diagnosis: other cases of hydrothorax, exudative pleuritis; ^c Chi Square test; ^d T-test for Equality means *The significance level is 0.05

mean (SD) age of patients with COVID-19-related pleural disorders on mechanical ventilation was 70.67±13.31 years, as shown in Table 1.

In total, 18 (40.0%) patients with COVID-19-related pleural disorder(s) had a fatal outcome. In terms of gender, eight of 17 (47.0%) female patients died and ten of 28 (35.7%) male patients had the same outcome. We found no statistical significance between these two groups ($p=0.451$). In terms of age groups, patients with COVID-19-related pleural disorder(s) that were over 60 years old were most susceptible to death, i.e. in 14 (56.0%) out of 25 patients in this age group. Out of 21 patients with pneumothorax and pneumothorax with either subcutaneous emphysema, pleural effusion, pneumomediastinum, cystic lungs, pleural empyema, or serial rib fracture, 12 (57.0%) patients died. More than half of patients with bilateral pleural complications had a

fatal outcome as well, i.e. in five (55.5%) of nine patients. Moreover, almost half of patients with two pleural complications died, i.e. three (43.0%) out of seven patients. All 11 patients (100.0%) that were placed on mechanical ventilation eventually died, the same outcome was reported in seven out of 34 patients treated without mechanical ventilation, and statistical significance between these two groups of patients was found $p=0.000$, as seen in Table 2.

5. DISCUSSION

COVID-19 was a global outbreak of coronavirus, with the first case described in the Chinese city of Wuhan in December 2019. Since then, there are more than 6.8 million deaths reported worldwide, many attributed to severe cases of pneumonia and acute respiratory distress syndrome (ARDS). Increased alveolar-capillary

membrane permeability, resulting in edema, impaired gas exchange, and consequently respiratory failure due to severe hypoxemia, are hallmark findings of ARDS. Approximately one-third of COVID-19 victims developed ARDS, and 53% of COVID-19-related ARDS fatal outcomes were caused primarily by respiratory failure (5). Radiological findings include bilateral patchy ground-glass opacities with a predominantly peripheral distribution, whereas pleural complications are still considered uncommon. Even though parenchymal findings have received more attention, pleural involvement has been shown to be associated with disease severity and overall prognosis (6). One systematic review of imaging findings in 919 patients, conducted by Salehi and colleagues, reported pleural effusion and pneumothorax to be late features that most likely represent disease progression (7).

Our study included 45 patients (1%) among the total number of 4520 RT-PCR-positive patients, who had at least one radiologically verified COVID-19-related pleural disorder. Tube thoracostomy is considered a successful approach in the non-operative management of excess fluid and air in patients with unilateral or bilateral pleural complications. We performed tube thoracostomy in 84.4% of patients with unilateral pleural complications, whereas in 11.1% of patients, chest tubes needed to be placed on both sides. Most critically ill patients (mechanically ventilated) with pneumothorax eventually require some type of thoracoscopic intervention—chest tube placement (tube thoracostomy), thoracentesis, pectoral incisions for subcutaneous emphysema, etc.

The indications for the intensive care unit (ICU) admission vary in many countries due to their admission criteria. According to the initial studies in Wuhan, performed by Meng and his colleagues, the clinical progression from the initial symptoms to pneumonia is about five days, and the median time to ICU admission from the start of hypoxemia is seven to 12 days (8). For patients with pleural effusion as a consequence of a COVID-19 infection, intubation from the onset of symptoms was 3.00 ± 0.00 days; for ones with pneumothorax 13.44 ± 11.38 days; for patients with other COVID-19-related pleural disorders 27.00 ± 0.00 days—in total, 13.73 ± 11.53 days if we consider all COVID-19-related pleural disorders in mechanically ventilated patients.

Several studies have shown that rates of invasive mechanical ventilation among patients admitted to ICU settings range from 29.1% to 89.9% (9, 10). In our study, 11 (24.4%) patients out of 45 with COVID-19-related pleural disorder(s) had to be placed on mechanical ventilation during their hospital stay in the ICU. Eight patients (88.9%) out of nine who were on mechanical ventilation and had a pneumothorax required a thoracoscopic intervention (tube thoracostomy and/or thoracentesis and/or pectoral incisions); one additional patient with other COVID-19-related pleural disorders also required surgical treatment—in total, out of 11 patients who were on mechanical ventilation at the ICU, nine of them (81.8%) were surgically treated.

In our retrospective study, 18 (40.0%) patients with COVID-19-related pleural disorder(s) died. Gender-wise, eight out of 17 (47.0%) female patients died whereas ten of 28 (35.7%) male patients had the same outcome. Most notably, all 11 patients (100.0%) that were placed on mechanical ventilation eventually died. The same outcome was reported in seven out of 34 patients that were not mechanically ventilated.

In one retrospective observational cohort study, performed within the University of Pennsylvania Health System and published in June 2022, patients were divided into two cohorts based on the presence/absence of at least one tube thoracostomy during the first COVID-related admission to the ICU. Patients who received chest tubes had increased mortality, longer duration of mechanical ventilation, and overall hospital and ICU length of stay compared with those patients who did not develop a pneumothorax requiring chest tube placement (11). Authors of the same study recognized the necessity for a tube thoracostomy as a negative prognostic sign.

Barotrauma is considered a relatively common complication due to mechanical ventilation, and pneumothorax was reported in approximately 25% of COVID-19 patients. The majority of patients with severe COVID-19-related pleural effusion or pneumothorax will eventually require a tube thoracostomy. Future research should be directed toward the assessment of long-term pulmonary consequences in patients who had COVID-19, with the development of strategies to withstand and treat potential consequences of similar viral infections in the future.

6. CONCLUSION

COVID-19-related disorders are underappreciated and relatively rare findings that most likely represent disease progression. Tube thoracostomy is the mainstay of treatment of COVID-19-related pleural disorders, both in non-mechanically-ventilated patients as well as in the ICU setting. In critically ill patients, however, tube thoracostomy is considered a negative prognostic sign.

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