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PNEUMOTHORAX IN COVID-19 – A NEW CHALLENGE

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Abstract

Background: Coronavirus disease 2019 mainly affect the lungs which can complicate to pneumothorax and require hospitalization. We aimed to discuss the presence of pneumothorax and its possible risk factors in vulnerable patients of COVID-19 to establish an effective preventive and therapeutic strategy for this fatal complication.

Methods: This retrospective observational study included 30 admitted patients of COVID-19 associated pneumothorax. The patient's data concerning demography, clinical manifestation, associated medical illness, point of onset of pneumothorax, mode of oxygenation with FiO2 and PEEP, radiological imaging, and outcome were extracted from their medical records. All collected data were tabulated, compiled, and analyzed to establish possible causality of pneumothorax.

Results: All patients of the study group exhibited symptomatic presentations, 73% of patients had the severe clinical conditions and 24 patients also had associated chronic medical illness. In our study pneumothorax developed 3rd week onwards after symptoms onset with a mean time of pneumothorax was found to be 23.96 days (23.96±8.06). At the point of diagnosis of pneumothorax, 22 patients were on non-invasive ventilation, 6 on high flow mask, and 2 patients on invasive ventilation, these patients required higher FiO2 (77.66%) and higher PEEP (10.83 cmH2O) to maintain PaO2 within normal range. All patients had raised COVID-related inflammatory markers viz. NLR, D-dimer, CRP, IL-6, and these markers showed a positive correlation with the duration of hospital stay in patients of pneumothorax.

Conclusion: Pneumothorax can be suspected in COVID-19 infected patients having severe COVID-19 pneumonia of longer duration with assistant ventilation and raised inflammatory markers going to rapid worsening of symptoms.

Keywords: Assistant ventilation, COVID-19, Inflammatory markers, Pneumothorax

Key Message: Why does pneumothorax predispose to ventilated COVID-19 patients? Why few patients of COVID-19 are more vulnerable to developing pneumothorax? Hence this study aimed to discuss the presence of pneumothorax and its possible risk factors in vulnerable patients of COVID-19 and to establish an effective preventive and therapeutic strategy for this fatal complication.

Introduction

Coronavirus disease 2019 (COVID-19) is a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The most common clinical manifestation of COVID-19 positive patients includes fever, cough, and shortness of breath. The complications of COVID-19 include pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, septic shock, disseminated intravascular coagulation, and pneumothorax (1,2). Radiological imaging plays an important role in the diagnosis and follow-up of Covid-19 pneumonia (3). Common High-resolution computerized tomography (CT) findings in COVID-19 are of patchy ground-glass opacities with a peripheral or posterior distribution, mainly involving the lower lobes (4). Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, CT halo sign, and pneumothorax are some of the uncommon but possible findings seen with disease progression (5). Pneumothorax has been reported in a few patients with COVID-19, although the significance and frequency of this association remain unclear. More recently, Pneumothorax has been noted in complicated cases of COVID-19 requiring hospital admission and the rate of pneumothorax and pneumomediastinum in ventilated patients has been reported as 15% (6). In this study, we aimed to describe the clinical characteristics of patients with the management protocol and consider whether the development of pneumothorax can be used as a marker of poor prognosis.

METHODS

Study Design: The present retrospective observational study was conducted on 30 moderates to critical ill *COVID-19* positive patients complicated with pneumothorax, admitted to S.M.S. Medical College and Attached Hospitals, Jaipur, India from 1st April 2021 to 31st

May 2021. This study was approved by the Institutional Ethics Committee of our institution. In this study we include RT-PCR positive patients for SARS-CoV-2 with pneumothorax and/or pneumomediastinum during course of hospitalization. These patients undergone serial observation to collect data till discharge from hospital.

Data Collection: COVID-19 were diagnosed based upon World Health Organization interim guidelines [7]. The patient information regarding demographic data, medical history, clinical manifestation, laboratory findings, chest radiograph (CXR) findings, high-resolution computed tomography (HRCT) scans of chest of available patients and oxygen support at presentation were extracted from the medical records for data analysis. In this study, severity of COVID-19 patients decided as per the Indian Council of Medical Research (ICMR) guidelines. Severely ill category had COVID-19 positive patients with clinical signs of pneumonia (fever, cough, shortness of breath, fast breathing) with respiratory distress and SpO2 <90% on room air. Critically ill category had COVID-19 positive patients with clinical signs of severe pneumonia and radiological evidence of bilateral opacities in chest with respiratory failure and COVID-19 related complication like acute respiratory distress syndrome (ARDS), sepsis, septic shock etc., after exclusion of other causes. Laboratory test include total leukocyte count (TLC), Neutrophil-Lymphocyte ratio (NLR), D-dimer, C-reactive protein (CRP) and interleukin-6 (IL-6). Required oxygen support tool for maintenance included high flow mask, non-invasive ventilation (NIV) and invasive ventilation. Chest radiograph and HRCT chest evaluated for CT severity score and pneumothorax and /or pneumomediastinum. (*Assigned out of 25 based on the percentage area involved in each of the 5 lobes*) [8]. Affected side of lung and time of onset of pneumothorax were collected from medical records. Duration of hospital stays and final outcome were collected. Patients who had incomplete medical records were excluded from study. The data was compiled, tabulated, interpreted for factors predisposing pneumothorax in COVID-19 infection.

Statistical analysis: Quantitative data was expressed as mean and standard deviation. Qualitative data was expressed as proportions. The level of significance was assigned at p-value less than 0.05. Statistical Package for the Social Sciences (SPSS) and R program was used for statistical analysis.

Results (Table 1 & 2):

A total of 30 COVID-19 patients with pneumothorax and/or pneumomediastinum were included in this study. The mean age of SARS-CoV-2 infected patients with pneumothorax was 47.63 year (47.63 ± 9.64). Male patients (60%) were affected more by pneumothorax as compared to female patients (40%). All patients had COVID-19 related major clinical symptoms at hospitalization including fever, cough and shortness of breath. Most of pneumothorax associated COVID-19 patients presented in hospital in 2nd week and mean time duration of hospitalization after symptoms onset was 9.9 days (9.9 ± 1.9). As per clinical severity of COVID-19, 10% patients were moderate, 73% patients were severe and 17% patients were in critical condition. In our study, 24 patients had history of underlying chronic medical illness among which 14 patients had past history of pulmonary pathology (Bronchial asthma, COPD, pulmonary tuberculosis, Lung abscess) while 10 patients had history of other non-communicable disease (Diabetes mellitus, hypertension, coronary artery disease).

Table 1: Demographic, clinical and management details in patients of pneumothorax associated with COVID-19 for quantitative data

Quantitative data	Mean ± SD
Age (Year)	47.63 ± 9.64
Duration of illness (Days)	9.9 ± 1.9
Duration of pneumothorax (Days)	23.96 ± 8.06
Required FiO2 (%)	77.66 ± 17.79
Required PEEP (cmH2O)	10.83 ± 1.73
WBC ($x10^3/mm^3$)	15.18 ± 3.59
NLR	7.23 ± 1.77
CRP (mg/L)	43.67 ± 19.64
D-DIMER (µg/mL)	2385.27 ± 1337.92
IL-6 (pg/mL)	53.44 ± 44.30
Duration of Hospital Stay (Days)	40.5 ± 20.13

Abbreviation: FiO2: Fraction of inspired oxygen; PEEP: Positive end expiratory pressure; WBC: white blood cells; NLR: Neutrophil-Lymphocyte ratio; CRP: C-reactive protein; IL-6: interleukin-6: SD: Standard Deviation

Table 2: Demographic, clinical and management details in patients of pneumothorax associated with COVID-19 for qualitative data

Qualitative Data	Numbers (N=30)	Percentage
Sex		
Male	18	60%
Female	12	40%
Severity of disease		
Moderate	3	10%
Severe	22	73%
Critical	5	17%
Comorbidity	24	80%
Lung Involvement	14	58%
Other System involvement	10	42%
Time duration of pneumothorax		
3rd Week	14	47%
4th Week	9	30%
5th week onwards	7	23%
Acute Symptoms		
Chest Pain	30	100%
Increased SOB	30	100%
Affected Side of Lung		
Unilateral	25	83%
Bilateral	5	17%
Mode of Oxygenation		
High flow Mask	6	20%
NIV	22	73%
Intubated	2	7%
Outcome		
Live	21	70%
Death	9	30%

Abbreviation: Data are represented as number (N) and percentage (%); SOB: Shortness of breath; NIV: Non-invasive ventilation;

Table 3: Correlation of duration of hospital stay with demographic, clinical and laboratory parameters

Parameters	'r' Value	P-value
Age	0.7281	0.0008
Duration of illness	0.1004	0.665
Interval of pneumothorax	0.6918	0.0005
FiO2 to maintain PaO2	0.6595	0.0011
PEEP	0.5677	0.0072
WBC	0.4947	0.0226
NLR	0.5167	0.0164
CRP	0.694	0.0005
D-DIMER	0.5341	0.0126
IL-6	0.4266	0.0537

Abbreviation: 'r': correlation coefficient; P values indicate differences between two parameters. P < .05 was considered statistically significant; FiO2: Fraction of inspired oxygen; PaO2: partial pressure of oxygen; PEEP: Positive end expiratory pressure; WBC: white blood cell; NLR: Neutrophil-Lymphocyte ratio; CRP: C-reactive protein; IL-6: interleukin-6

Pneumothorax after symptoms onset in hospitalized patients were noted in 3rd week onwards. In this study 47% patients had pneumothorax in 3rd week, 30% patients in 4th week while 23% patients had pneumothorax in 5th week onward of symptoms onset. Mean duration of pneumothorax after symptoms onset were found to be 23.96 days (23.96 ± 8.06). All patients of study population had acute onset of chest pain and exacerbation of shortness of breath at the point of diagnosis of pneumothorax. Diagnosis of pneumothorax in pre-existing COVID-19 pneumonia were confirmed by chest radiograph and HRCT chest (Figure 1 & 2). Radiological imaging showed unilateral pneumothorax in 83% patients and bilateral pneumothorax in 17% of COVID-19 infected patients

while 3 patients also detected associated pneumomediastinum (Figure 1C & 2C). At the time of diagnosis of pneumothorax, 22 patients were on non-invasive ventilation (NIV), 6 patients were on high flow mask (HFM) while 2 patients had invasive ventilation with endotracheal intubation. Average FiO2 required to maintain oxygen saturation within normal range was found to be 77.66% (77.66 ± 17.79). 24 patients required assistant ventilation to maintain PaO2 within normal range. Average PEEP required in these patients was found to be 10.83 cmH2O (10.83 ± 1.73).

All patients of study population screened for available COVID related inflammatory markers. Mean white blood cell counts were found to be 15.18 $x10^3/mm^3$ (15.18 ± 3.59). Serum level of Neutrophil-Lymphocyte ratio (NLR) was raised with mean value of 7.23 (7.23 ± 1.77). All selected patients had raised absolute value of CRP, D-dimer and IL-6 with mean value of 43.67 mg/L (43.67 ± 19.64), 2385.27 µg/mL (2385.27 ± 1337.92) and 53.44 pg/mL (53.44 ± 44.30) respectively. In this retrospective study of 30 patients who had developed pneumothorax, 21 patients (70%) survived successfully and discharged to home while 9 patients (30%) succumbed to life due to pneumothorax and/or other COVID related complications. Mean duration of hospital stay for patients of pneumothorax was found to be 40.5 days (40.5 ± 20.13) while patients who survived by this fatal complication was discharged by an average duration of 48.71 days.

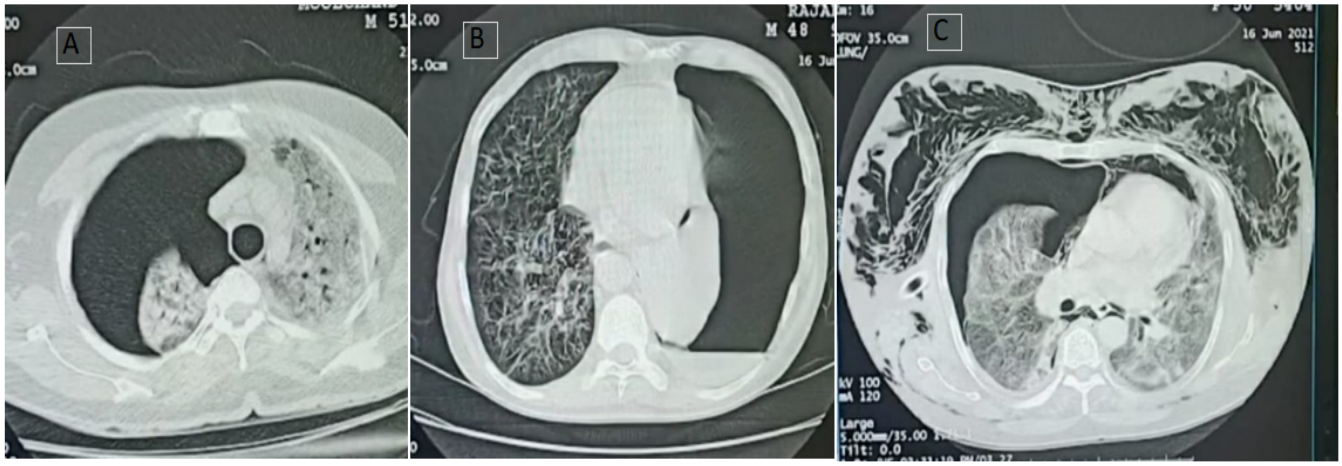

Figure 1: *(A) Right pneumothorax with passive collapse of lung with left shift of mediastinum with gross ARDS in right lung in patients of COVID-19 on NIV; (B): Left hydropneumothorax due to rupture of lung abscess in pleural cavity with consolidation and septal thickening in right lung, this patient is on high flow mask and in recovery phase; (C): Right pneumothorax and pneumomediastinum with subcutaneous emphysema with ARDS in left upper lobe.*

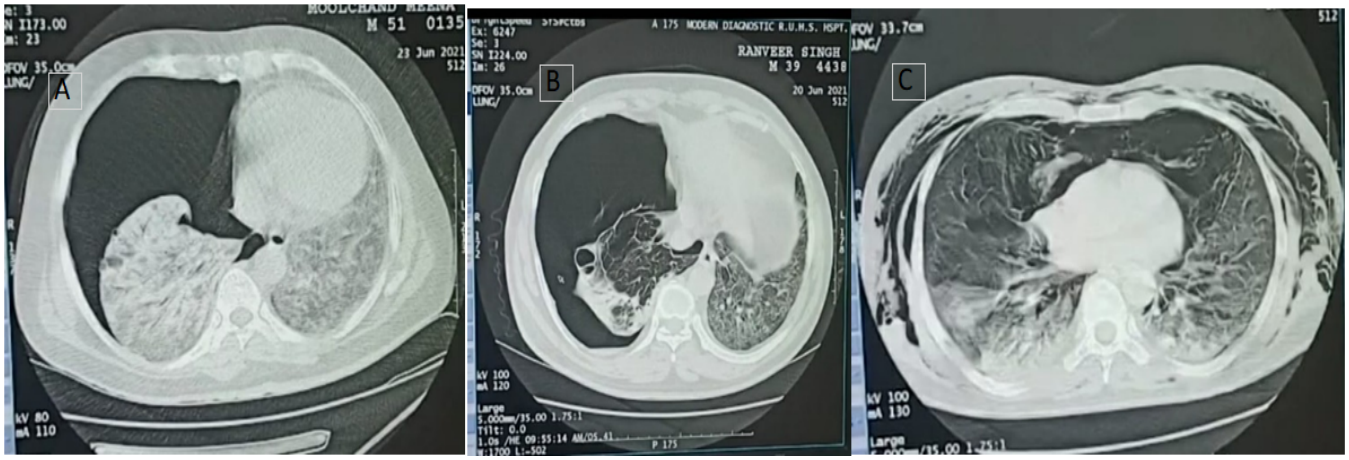

Figure 2: *(A) Right pneumothorax with passive collapse of lung with left shift of mediastinum with gross ARDS in right lung in patients of COVID-19 on invasive ventilation; (B): Right pneumothorax with associated precipitating bullous cystic lesions with left shift of mediastinum with gross ARDS in right lung at 5th week of symptoms onset in patients of COVID-19 on intermittent NIV and high-flow mask; (C): Pneumomediastinum with bilateral ground glass opacities with subcutaneous emphysema at 2nd week of onset of symptoms and this patient died after 5 days of diagnosis of pneumothorax.*

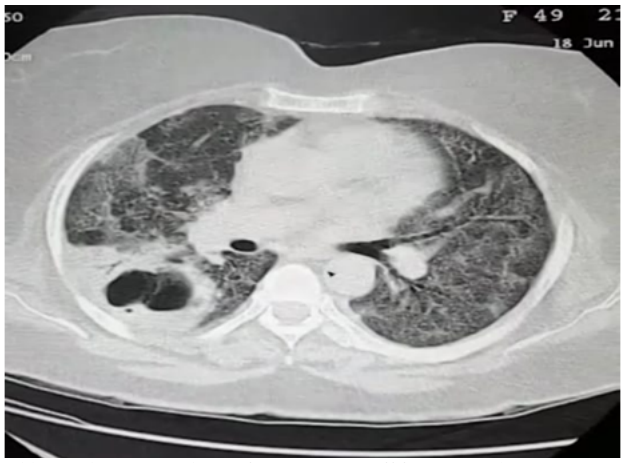

Figure 3: *48 year old female, developed lung abscess 15 days after weaning off from NIV, later on patient suddenly deteriorate and developed hydropneumothorax, pleuro-pulmonary fistula, subcutaneous emphysema and recurrent pneumothorax.*

In this study, among survivor patients we also try to establish a correlation between duration of hospital stay with various quantitative parameters of selected study sample, which indirectly suggest factors influencing time taken to recovery from pneumothorax (Table 3). Time taken to discharge from hospital had statistically positive correlation with age of patients ('r' = 0.7281, p = 0.0008), hence older patients stay longer in hospital as compared to younger age group. Those patients who developed pneumothorax in later stage of hospitalization was discharged late with a statistically significant positive correlation ('r' = 0.6918, p =0.0005). Patients who required higher FiO2 and PEEP at the time of pneumothorax to maintain adequate PaO2 was discharged late from hospital with a statistically significant positive correlation ('r' = 0.6595, p =0.0011 for FiO2 and 'r' = 0.5677, p =0.0072 for PEEP). In this study, patients who had higher blood level of total leukocyte count, NLR, CRP and D-dimer was stay longer in hospital with a statistically significant positive correlation ('r' = 0.4947, p =0.0226 for WBC, 'r' = 0.5677, p =0.0072 for NLR, 'r' = 0.694, p =0.0005 for CRP and 'r' = 0.5341, p =0.0126 for D-dimer). Duration of hospital stay not significantly correlated with duration of illness and serum level of IL-6.

Discussion:

In this study, we evaluate the existence of pneumothorax in the context of COVID-19 that includes ventilated patients. We also try to establish an association between COVID-19 induced pneumothorax and its precipitating factors. An observational study cannot establish causality between COVID-19 and pneumothorax. Explaining the association between COVID-19 and pneumothorax is more challenging. Radiology frequently showed typical changes of COVID-19, although in three cases lung cavitation was detected, which is likely to be a possible cause of pneumothorax (Figure 3). Cyst formation in the lungs was first noted as a radiological consequence of COVID-19 and has been corroborated by studies demonstrating radiological progression from areas of consolidation to bullae (9-11). Previously reported cases have found that cyst formation is not restricted to patients receiving positive-pressure ventilation, suggesting that barotrauma alone cannot account for these findings (10). Likewise, the fact that we report six cases of pneumothorax in patients who have not undergone assistant ventilation in the form of NIV and invasive ventilation suggests that barotrauma alone cannot explain this association. Additionally, cyst formation has been noted as a late consequence of ARDS due to COVID-19, the disease processes postulated including ischemic parenchymal damage and inflammation (12). In terms of critical-care admissions, previous analysis of intubated patients with SARS noted that tachypnoea at admission, hypoxemia, and hypercapnia all correlated with the development of pneumothorax (13). Understanding the mechanism of the association between COVID-19 and pneumothorax is required for the development of preventative interventions.

Our study suggests that pneumothorax mostly occurred in young adults ranging from 3rd to 6th decades with an average age was found to be 47.6 years. Our study suggests the pneumothorax in COVID-19 is more prevalent in males as compared to female patients. (Male: female 3:2); A large series of patients with COVID-19 suggest that male patients are more commonly affected by severe forms of the disease, which may account for this observation (7). This study suggests that symptomatic patients with late hospitalization are more prone to the development of pneumothorax as shown by compiled data that all patients of this study group had a symptomatic presentation in the form of fever, cough, and shortness of breath as well as the majority of pneumothorax associated COVID-19 patients presented in hospital in 2nd week and mean time duration of hospitalization after symptoms onset was 9.9 days. As per the clinical severity of COVID-19, nearly three fourth of patients had severe COVID-19 which suggest that late presentation with severe COVID-19 patient is more prone to develop pneumothorax. Pulmonary progression of COVID-19 according to severity and duration of disease

responsible for the formation of bullous and cystic lesion in lung parenchyma which leads to a pneumothorax (Figure 2B). Other possible causative factors for pneumothorax in COVID-19 may be persistent coughing resulting in increased intrathoracic pressure in the presence of underlying pleural abnormalities or alveolar damage from COVID-19 pneumonia-related inflammation or ischemic parenchymal damage (14). Past history of the diseased lung in the form of bronchial asthma, COPD, pulmonary tuberculosis, lung abscess, etc. was found to be major risk factors for COVID-19 associated pneumonia as evidenced by this study that 50% of patients had underlying chronic pulmonary pathology. Pneumothorax is a surgical emergency that required immediate attention in rapidly deteriorating COVID-19 patients. Pneumothorax is a late complication in ventilated patients of COVID-19 as evidenced by this study that nearly 80% patients of with pneumothorax were diagnosed in the 3rd and 4th week of onset of symptomatic disease. The mean duration of pneumothorax after symptoms onset was found to be 23.96 days. In this study nearly 40% patients of with pneumothorax had been found in their recovery phase as evidenced by a reduction in FiO2, these patients suddenly deteriorate and worsen clinically by acute chest pain and exacerbation of shortness of breath.

This study suggests that the pneumothorax must be considered as a differential in an acutely deteriorating patient with persistent hypoxia in Covid-19. The other important differential to consider is the possibility of a pulmonary embolism as several studies highlight its association with COVID-19 (15). Pulmonary thrombo-embolism can also result in parenchymal cavitation with subsequent pleural rupture leading to a pneumothorax as evidenced clinically by electrocardiography in the form of sinus tachycardia and Q3S1T3 pattern in 9 patients. However, no radiological evidence of pulmonary thromboembolism was detected in this study due to lack of CTPA and impaired visualization of fresh lobar pulmonary infarct due to pneumothorax. The significance of identifying such secondary pathologies in COVID-19 is vital as the treatment required is very different, with possible life-threatening consequences in case the incorrect diagnosis or management is initiated. The majority of patients (83%) had unilateral pneumothorax suggesting local cystic lesions was act as an important causative factor for the development of pneumothorax. At the point of diagnosis of pneumothorax majority of patients (73%) were on non-invasive ventilation supported with PEEP. In this study, 6 patients were on a high-flow mask at the point of diagnosis of pneumothorax suggesting that barotrauma by assistant ventilation is not only a single precipitating factor for pneumothorax. Radiologically three patients had lung abscess which was ruptured in the pleural cavity to produce pneumothorax. At the point of diagnosis of pneumothorax, most of the patients required high FiO2 and high PEEP to maintain PaO2 with an average FiO2 77.6% and average PEEP of 10.83 cmH2O which leads to rupture of inflamed alveoli and visceral pleura and leaking of air in the pleural cavity.

In a case series of 6 patients with SARS and pneumothorax from Hong Kong, administration of corticosteroids was thought to affect lung healing, and the presence of a higher peak serum LDH and peripheral leukocyte count was postulated to depict a greater extent of lung injury thus raising the risk of pneumothorax (16). In our study, all patients were on treatment with steroids and have elevated blood levels of total leukocyte count, neutrophil-lymphocyte ratio, CRP, D-dimer, and IL-6. This suggests that increased inflammatory parameters have a major risk factor for the development of pneumothorax in patients of COVID-19. In this retrospective study of 30 patients who had developed pneumothorax, 21 patients (70%) survived successfully and were discharged to home while 9 patients (30%) succumbed to life due to pneumothorax and/or other COVID related complications. Succumbed patients died within 1st week of the development of pneumothorax as a consequence of ARDS and respiratory failure. 70% of patients of with pneumothorax fight this fatal complication and survived; these patients' stay in the hospital for a longer duration with an average duration of discharge from the hospital was found to be 48.71 days. The duration of hospital stay in these surviving patients also depends upon various parameters. Older age patients were discharged later from the hospital. In this study, patients who had higher blood levels of total leukocyte count, NLR, CRP, and D-dimer was stay longer in the hospital with a statistically significant positive correlation. Duration of hospital stays reduced in patients of COVID-19 associated pneumothorax by effective control of inflammatory markers. Management of pneumothorax in COVID-19 patients necessitating an intercostal chest drainage tube based on the British thoracic society's (BTS). BTS further recommends that bubbling chest drains should be considered for strategies to minimize droplet exposure via the chest drain circuit. This can be achieved by connecting the chest drain to wall suction (even in cases where suction is not normally indicated but set at a very low level such as 5cmH2O) thereby creating a closed system or by installing a viral filter onto the suction port of a Rocket chest drain bottle. Digital drain circuits are an alternative method of reducing the risk of droplet spread, but they do not contain a viral filter (17).

Conclusion:

Our study highlights pneumothorax as a complication of COVID-19 pneumonia. Pneumothorax may develop in COVID-19 pneumonia due to multiple plausible mechanisms. These may include injury of the lung parenchyma, inflammation, ischemia, infarction, cough, and rupture of cystic lung lesion. This study highlighted various vulnerable populations of COVID-19 progressing to pneumothorax. Our study is a reminder that an acute

deterioration with a rapid oxygen desaturation in a COVID-19 patient could indicate a pneumothorax with differential diagnosis of pulmonary thromboembolism. Pneumothorax can be suspected in COVID-19 infected patients having severe COVID-19 pneumonia of longer duration with assistant ventilation and raised inflammatory markers going to rapid worsening of symptoms. Therefore, clinicians should be aware that a pneumothorax can be observed within the radiological and clinical manifestations of COVID-19 pneumonia and it may lead to an increase in mortality or morbidity.

Limitation: There are several limitations to this study. The number of patients was rather limited and needs to be studied on a larger patient cohort. It was a single-center retrospective observation study and a comparative sample population could not be available.

Ethical approval: This study approved by ethical and research committee of SMS medical college and Hospital, Jaipur, India.

Author contributions: S. Bhandari, G. Rankawat and A. Singh formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; G. Rankawat and A. Singh collected and analyzed data for study. G. Rankawat write the manuscript. S. Bhandari conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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