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Research Article

A Comparative Evaluation of Pneumothorax in Ventilated Patients of COVID-19

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Abstract

Background: Coronavirus disease 2019 can complicate into pneumothorax and need hospitalization. We aimed to discuss the presence of pneumothorax and its possible causality in vulnerable patients of COVID-19 to set up an effective preventive and therapeutic strategy for this fatal complication.

Methods: This retrospective observational case-control study included a total of 90 admitted patients of COVID-19 supported with NIV ventilation. 45 patients had a pneumothorax and another 45 had without pneumothorax as a control group. The patient's data concerning demography, clinical profile, point of onset of pneumothorax, required FiO2, PEEP, radiological imaging, and outcome were extracted from their medical records. All collected data were tabulated, compiled, and analyzed to establish the possible causality of pneumothorax.

Results: Patients of both groups had matched demographic and clinical symptoms. Patients with pneumothorax had late hospitalization (10.04 v/s 7.11 days), require high PEEP (10.46 v/s 8.71 cmH2O), had raised inflammatory markers (NLR 7.46 v/s 6.23; CRP 44.04 v/s 32.73; D-dimer 2311 v/s 1801 µg/mL), high mortality (26.67% v/s 8.89%) and longer hospital stay (50.66 v/s 37.88) as compared to control group of without pneumothorax with p-value < 0.05. In our study pneumothorax developed 3rd week onwards after symptoms onset with a mean time of pneumothorax was found to be 22.04 days.

Conclusion: Pneumothorax in COVID-19 infected patients of intensive care unit can be precipitated by severe COVID-19 pneumonia of longer duration with late hospitalization with high PEEP and raised inflammatory markers going to rapid worsening of symptoms.

Keywords: *COVID-19; Inflammatory Markers; Pneumothorax; Non-Invasive Ventilation*

Introduction

Coronavirus disease 2019 (COVID-19) is a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). COVID-19 positive patients mostly presented with fever, cough, and shortness of breath. The complications of COVID-19 include pneumonia, pulmonary thromboembolism, acute respiratory distress syndrome (ARDS), multi-organ failure, septic shock, and pneumo-

thorax [1,2]. Radiological imaging of the thorax has diagnostic as well as prognostic importance for COVID-19 related lungs disease. Common High-resolution computerized tomography findings in COVID-19 are of patchy ground-glass opacities with a peripheral or posterior distribution, mainly involving the lower lobes [3]. COVID-19 related pleural effusion, cavitation, CT halo sign, and pneumothorax are uncommon but possible findings of disease progression [4]. 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 assistant ventilation and the rate of pneumothorax and pneumomediastinum in ventilated patients has been reported as 15% [5].

Aim of the Study

In this study, we aimed to describe the clinical characteristics of patients with pneumothorax with the management protocol and various risk factors which predispose for pneumothorax in the vulnerable population of COVID-19.

Methods

Study design: The present retrospective observational case-control study was conducted on 90 COVID-19 positive patients of non-invasive ventilation (NIV), admitted at intensive care unit of S.M.S. Medical College and Attached Hospitals, Jaipur, India from 15th April 2021 to 15th June 2021. This study was approved by the Institutional Ethics Committee of our institute. In this study, we include 45 COVID-19 positive patients of NIV with pneumothorax as case and another 45 COVID-19 positive patients of NIV without pneumothorax as control. These patients underwent serial observation to collect data till discharge from hospital.

Data collection: COVID-19 were diagnosed based upon World Health Organization interim guidance [6]. The patient information about demographic data, medical history, clinical presentation, laboratory investigations, high-resolution computed tomography (HRCT) scans of the chest, duration of hospital stay, and final outcome was extracted from the medical records for data analysis. In this study, the severity of COVID-19 patients was decided as per the Indian Council of Medical Research (ICMR) guidelines. Duration of illness and days on which patients were put on NIV after hospitalization were extracted from the medical record. In this study, we selected those patients, which required NIV support. Data of NIV settings like FiO_2 and PEEP was collected at the time of pneumothorax in cases while for the control group greatest values of FiO_2 and PEEP were collected from the medical records for this study. For patients of COVID-19 associated pneumothorax, we extract data regarding the time duration of pneumothorax after hospitalization and the affected side of the lung. Laboratory tests include total leukocyte count (TLC), Neutrophil-Lymphocyte ratio (NLR), D-dimer, C-reactive protein (CRP), and interleukin-6 (IL-6). HRCT chest and chest radiograph evaluated for CT severity score and pneumothorax and /or pneumomediastinum. Duration of hospital stays and final outcome were extracted, compiled, and compared among case and control. Patients who had incomplete medical records were excluded from the study. The data was compiled, tabulated, interpreted, and compared among cases of pneumothorax and control group to show a causal relationship 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 parameters were compared among different groups using chi-square test and z-score for significant differences. 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 and Graph 1)

A total of 90 COVID-19 patients were included in this study out of which 45 patients have pneumothorax and another 45 patients are without pneumothorax. In this study, we try to evaluate precipitating factors for pneumothorax in COVID-19 infected patients. Hence, we select matched control group to avoid the influence of variable demographic parameters. COVID-19 infected patients, ventilated from NIV, selected for the study group in the range of 30 to 65 years of age. The mean age of SARS-CoV-2 infected patients with pneumothorax was

47.17 years (47.17 ± 9.01) while in the control group it was 47.89 years (47.89 ± 8.99) without any statistically significant difference (p = 0.7053). Male patients were affected more in both cases as well as the control group (p = 0.8337). All patients had COVID-19 related major clinical symptoms at hospitalization including fever, cough, and shortness of breath. The severity of disease at hospitalization and underlying chronic medical illness was not significantly different in patients of pneumothorax and control group (p > 0.05). Meantime duration of hospitalization after symptoms onset was much more for patients of pneumothorax (10.04 days) as compared to control group (7.11 Days) with p-value < 0.001.

	Case (N = 45) (Pneumothorax)	Control (N = 45) (Without pneumothorax)	
Quantitative data	**Mean ± SD**	**Mean ± SD**	**P-Value**
Age (Year)	47.17 ± 9.01	47.89 ± 8.99	0.7053
Duration of illness (Days)	10.04 ± 2.06	7.11 ± 1.77	<0.001
Day on which taken on NIV (Days)	3.04 ± 1.93	3.42 ± 1.95	0.3554
Required FiO_2 (%)	76.53 ± 17.11	77.20 ± 15.24	0.8449
Required PEEP (cmH_2O)	10.46 ± 1.76	8.71 ± 2.02	<0.001
WBC (x103/mm^3)	14.98 ± 3.26	12.69 ± 3.22	0.0012
NLR	7.46 ± 1.79	6.23 ± 1.66	0.0011
CRP (mg/L)	44.04 ± 19.19	32.73 ± 17.97	0.0049
D-DIMER (µg/mL)	2311.51 ± 1262.21	1801.4 ± 1159.54	0.049
IL-6 (pg/mL)	51.88 ± 41.10	42.07 ± 37.46	0.2437
Duration of Hospital Stay in survivors (Days)	50.66 ± 10.75	37.88 ± 10.50	< 0.001

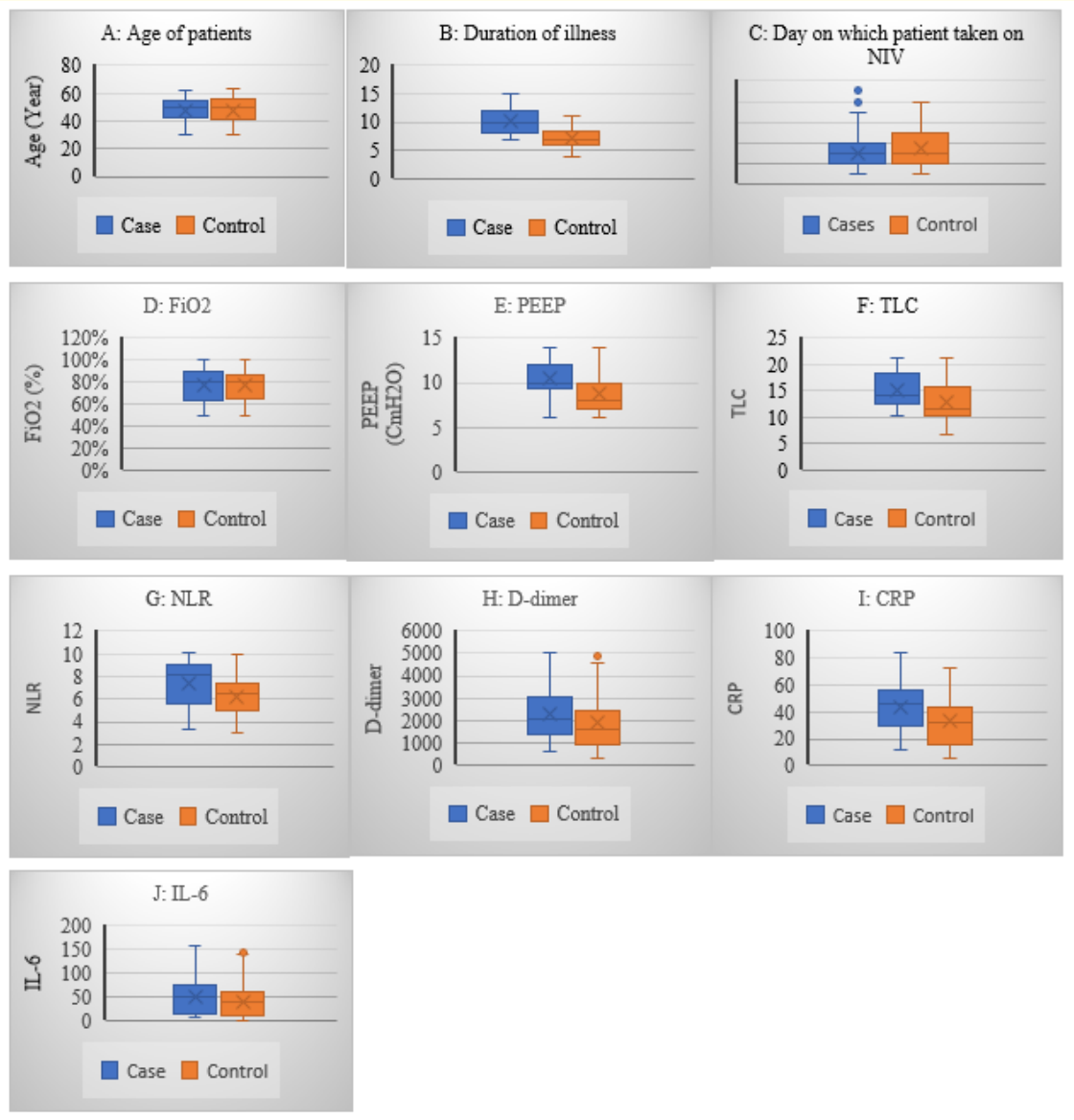
Table 1: *A comparative study of demographic, clinical and laboratory (Quantitative data) parameters in COVID-19 cases of pneumothorax and control group of without pneumothorax.*

Abbreviation: P values indicate differences between two parameters of case and control. P < .05 was considered statistically significant; SD: Standard Deviation; FiO_2: Fraction of Inspired Oxygen; PEEP: Positive End Expiratory Pressure; WBC: White Blood Cell; NLR: Neutrophil-Lymphocyte Ratio; CRP: C-Reactive Protein; IL-6: Interleukin-6.

	Case (N = 45) (Pneumothorax)	Control (N = 45) (Without pneumothorax)		
Qualitative Data	**Numbers (Percentage)**	**Numbers (Percentage)**	**Z-Value**	**P-Value**
Sex				
Male	25 (55.56%)	26 (57.78%)	0.2127	0.8337
Female	20 (44.44%)	19 (42.22%)		
Severity of disease				
Mild	0	2 (4.44%)	1.327	0.1835
Moderate	4 (8.89%)	8 (17.78%)		
Severe	41 (91.11%)	35 (77.78%)		
Comorbidity	34	34		
Lung Involvement	17 (50%)	11 (32.35%)	1.478	0.1388
Other System involvement	17 (50%)	23 (67.65%)		
Outcome				
Live	33 (73.33%)	41 (91.11%)	2.205	0.0271
Death	12 (26.67%)	4 (8.89%)		

Table 2: *A comparative study of demographic and clinical qualitative parameters in COVID-19 cases of pneumothorax and control group of without pneumothorax.*

Abbreviation: P values indicate differences between two parameters of case and control. P < .05 was considered statistically significant.



Graph 1: *A comparative evaluation of various quantitative parameters of patients of COVID-19 with pneumothorax as a case and patients of COVID-19 without pneumothorax as a control (A): Age of patients; (B): Duration of illness at hospitalization; (C): Day on which patient taken on NIV; (D): Required FiO2 on NIV to maintain PaO2; (E): Required PEEP on NIV to maintain PaO2; (F): Total leukocyte count; (G): Neutrophil-lymphocyte ratio; (H): D-dimer: (I): C-reactive protein; (J): IL-6.*

Patients of pneumothorax was taken on NIV on an average of 3.04 days (3.04 ± 1.93) after hospitalization while the control group was taken on NIV on an average of 3.42 days (3.42 ± 1.95) after hospitalization without any statistical significance difference (p = 0.3554). On NIV both groups required the nearly same amount of FiO_2 (76.53 ± 17.11% for cases and 77.20 ± 15.24% for the control group). Patients

of COVID-19 associated pneumothorax were required much higher PEEP of 10.46 cmH_2O (10.46 ± 1.76) as compared to the control group which required a lesser PEEP of 8.71 cmH_2O (8.71 ± 2.02) with p-value < 0.001. COVID-19 related inflammatory markers especially neutrophil-lymphocyte ratio (NLR), CRP, D-dimer and total leukocyte counts (TLC) was found to be significantly higher in cases of COVID-19 associated pneumothorax as compared to the control group viz. NLR 7.46 ± 1.79 v/s 6.23 ± 1.66 with p = 0.0011; CRP (mg/L) 44.04 ± 19.19 v/s 32.73 ± 17.97 with p = 0.0049; D-dimer (µg/mL) 2311.51 ± 1262.21 v/s 1801.4 ± 1159.54 with p = 0.049; TLC ($x103/mm^3$) 14.98 ± 3.26 v/s 12.69 ± 3.22 with p = 0.0012 for cases and controls respectively. Patients with COVID-19 associated pneumothorax had much higher mortality (26.67%) as compared to the control group which had lesser mortality (8.89%) with P = 0.0271. Among survivors of NIV, the duration of hospital stay was significantly higher (50.66 ± 10.75 days) for patients of pneumothorax as compared to the control group (37.88 ± 10.50 days) with p-value < 0.001.

COVID-19 associated pneumothorax was mostly observed in the 3rd and 4th week with an average duration of 22.04 days after ventilation with NIV. 73.33% patients of had unilateral pneumothorax, 17.78% of patients had a bilateral pneumothorax and 8.89% of patients had pneumomediastinum (Table 3).

NIV associated pneumothorax		
Qualitative Data	**Numbers**	**Percentage**
Time duration of pneumothorax		
2nd Week	2	4.44%
3rd Week	19	42.22%
4th Week	18	40.00%
5th week onwards	6	13.33%
Acute Symptoms		
Chest Pain	45	100.00%
Increased SOB	45	100.00%
Affected Side of Lung		
Unilateral	33	73.33%
Bilateral	8	17.78%
Pneumomediastinum	4	8.89%

Table 3: *Clinical and laboratory features in patients of COVID-19 associated pneumothorax which ventilated with NIV. Abbreviation: SOB: Shortness of Breath.*

Discussion

In this study, we evaluate the existence of pneumothorax in the intensive care unit of COVID-19 includes patients ventilated with NIV. We also try to establish an association between COVID-19 induced pneumothorax and its precipitating factors. This is a retrospective case-control observational study that includes an age-matched, gender-matched and underlying chronic medical illness matched control group in order to avoid these confounding factors for pneumothorax. Explaining the exact association between COVID-19 and pneumothorax is more challenging. Radiology frequently showed typical changes of COVID-19 and related complications. 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 [7-9]. Although cystic or bullous lesions in the lungs might be associated with high-pressure ventilation but not necessarily (Figure 1 and 2).

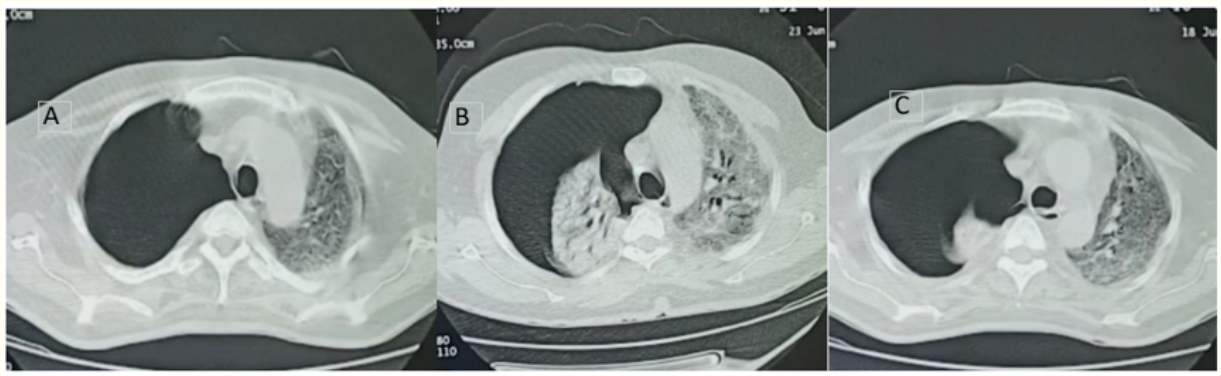


Figure 1: *(A) Right pneumothorax with left shift of mediastinum with gross ARDS in left lung in patients of COVID-19 on NIV; (B): Right pneumothorax with passive collapse lung with left shift of mediastinum with gross ARDS in left lung in patients of COVID-19 on NIV; (C): Right pneumothorax with passive collapse lung with left shift of mediastinum with gross ARDS in left lung in patients of COVID-19 on NIV.*

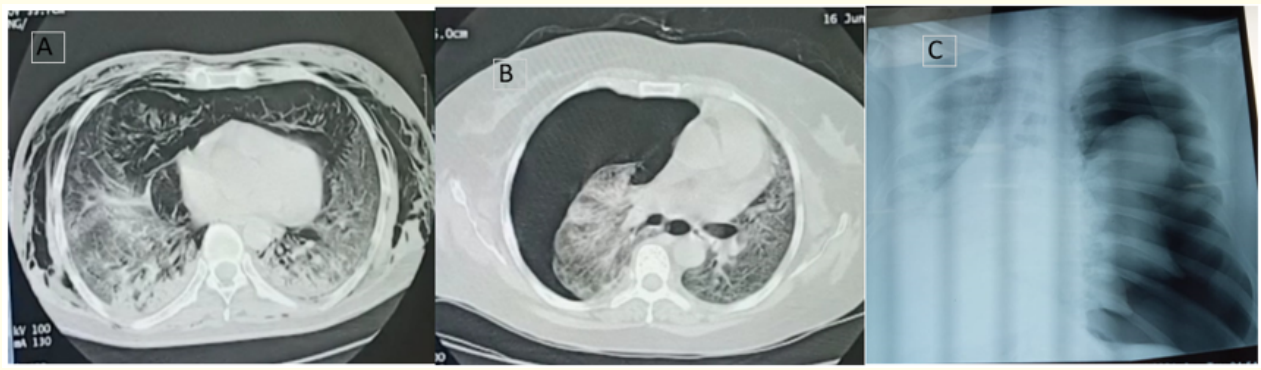


Figure 2: *(A) Pneumomediastinum with bilateral ground glass opacities with subcutaneous emphysema at 3rd week of onset of symptoms and this patient died after 3 days of diagnosis of pneumothorax; (B): Right pneumothorax with associated precipitating bullous cystic lesions with left shift of mediastinum with gross ARDS in right lung at 5th week of symptoms onset in patients of COVID-19 NIV; (C): Chest radiograph of COVID-19 patients on NIV have left pneumothorax with passive collapse of left lung with ground glass opacities in right lung.*

Previous 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 [8]. But, in this study, we included patients those required NIV as assistant ventilation to smooth comparison between both groups. Additionally, cyst formation has been noted as a late result of ARDS due to COVID-19, the disease processes postulated including ischemic parenchymal damage and inflammation [10]. In terms of critical-care admissions, an earlier analysis of intubated patients with SARS noted that tachypnoea at admission, hypoxemia, and hypercapnia all correlated with the development of pneumothorax [11]. 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 male adults ranging from 3rd to 6th decades with an average age was found to be 47.17 year and male to female ratio was 5:4. The Control group also had similar mean age and gender ratio without any clinically significant difference. 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 [6]. This study suggests that symptomatic patients at the time of hospitalization are more prone to the development of pneumothorax in general 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.

Most of pneumothorax associated COVID-19 patients presented in hospital in the 2nd week and mean time duration of hospitalization after symptoms onset was 10.04 days while this mean time duration of hospitalization was much lower (7.11 days) in the control group. This suggests that patients who were hospitalized in the early course of the disease did not have a pneumothorax. Hence, early hospitalization can prevent this life-threatening complication of pneumothorax in COVID-19 patients. As per the clinical severity of COVID-19, 91% of patients with pneumothorax had severe COVID-19 at the point of hospitalization while severity in the control group was lower (78% of patients were severe) but the difference was not statistically significant. Higher severity in patients of pneumothorax might be due to late presentation to the hospital which further procced these patients to COVID-19 related complications. Our study suggested that late presentation with severe COVID-19 patients 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 pneumothorax.

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 [12]. Past history of the diseased lung in the form of bronchial asthma, COPD, pulmonary tuberculosis, lung abscess etc. were found to be major risk factors for COVID-19 associated pneumonia as shown 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.

At the point of diagnosis of pneumothorax all the patients of the study population were on non-invasive ventilation supported with higher FiO_2 and PEEP. At the point of diagnosis of pneumothorax most COVID-19 patients had required high FiO_2 and high PEEP to keep up PaO_2 with an average FiO_2 of 76.5% and average PEEP of 10.46 cmH_2O which leads to rupture of inflamed alveoli and visceral pleura and leaking of air in the pleural cavity. Those patients which spared from a pneumothorax (control group) were supported with much lesser PEEP (8.71 cmH_2O) on NIV as compared to patients of pneumothorax (P-value < 0.001). Hence, higher PEEP in assistant ventilation is an important causative factor for pneumothorax. In this study given FiO_2 was found to be similar in both groups. To prevent pneumothorax, ventilation support must be set at lower PEEP and higher FiO_2 to maintain adequate oxygenation in patients of COVID-19. During weaning of NIV try to lower down PEEP as early as possible in compensation with higher FiO_2.

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 leucocyte count was postulated to depict a greater extent of lung injury thus raising the risk of a pneumothorax [13]. In our study, all patients were on treatment with steroids and have raised blood level of neutrophil-lymphocyte ratio, CRP, D-dimer, IL-6, and total leukocyte count. Mean value of NLR, CRP, D-dimer and TLC was much higher in patients with COVID-19 associated pneumothorax as compared to the control group. This suggests that increased inflammatory parameters have a major risk factor for the development of pneumothorax in patients of COVID-19. However, these inflammatory parameters had been also found to be raised from baseline in patients of the control group but the mean value of the inflammatory markers were found to be much higher in patients with pneumothorax as compared to patients without pneumothorax. So, we can prevent pneumothorax in these vulnerable populations by effective control of inflammation in body.

In this retrospective study, out of 45 patients who had developed pneumothorax, 33 patients (73.33%) survived successfully and were discharged to home while 12 patients (26.67%) succumbed to life due to pneumothorax and/or other COVID-related complications. On the other hand, the mortality rate was significantly lesser (8.89%) with a higher survival rate (91.11%) in patients without pneumothorax. Hence, pneumothorax itself is an important lethal complication of pneumothorax which leads to increase mortality in the intensive care unit of COVID-19. Succumbed patients died within 1st week of development of pneumothorax as a consequence of ARDS and respiratory failure. Those patients with a pneumothorax who survived this fatal complication of COVID-19 pneumonia stay in hospital for a longer duration with an average duration of discharge from the hospital was found to be 50.66 days, while patients of the control group were discharged earlier from the hospital with an average duration of hospital stay was found to be 37.88 days in patients without pneumothorax. Duration of hospital stay can be reduced in patients of COVID-19 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 reduce 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 5cmH_2O) 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 [14]. 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. 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. Pneumothorax is a late complication in ventilated patients of COVID-19 as shown by this study that nearly 82% patients of with pneumothorax diagnosed in 3rd and 4th week of onset of symptomatic disease. The mean duration of pneumothorax after symptoms onset was found to be 22.04 days. The most of patients (73%) had unilateral pneumothorax suggesting local cystic lesions was act as an important causative factor for the development of 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.

Conclusion

Our study highlights pneumothorax as a complication of COVID-19 pneumonia in a vulnerable population. Pneumothorax may develop in COVID-19 pneumonia due to multiple plausible mechanisms including injury of the lung parenchyma, inflammation, ischemia, infarction, cough, and rupture of cystic lung lesion. This study informed about the difference between precipitating factors in patients with pneumothorax and without pneumothorax. COVID-19 patients supported by NIV will be more prone for pneumothorax if the patient has late hospitalization, higher PEEP on NIV raised inflammatory markers. Patients with pneumothorax have higher mortality with longer hospital stays as compared to the control group. 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 late hospitalization with assistant ventilation and raised inflammatory markers going to rapid worsening of symptoms. Therefore, clinicians should be aware that a pneumothorax can be observed as the radiological and clinical manifestation of COVID-19 pneumonia and may lead to an increase in mortality and/or morbidity.

Limitation of the Study

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 possibility of recall bias couldn't be ruled out.

Ethical Approval

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

Author Contributions

S. Bhandari, G. Rankawat, A. Singh, and A. Lohmror 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 the study. G. Rankawat writes the manuscript. S. Bhandari and A. Lohmror 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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Availability of Data and Materials

Available from the corresponding author upon reasonable request.

Declaration of Competing Interest

All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential.

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