Journal of Acute Disease

Original Article

jadweb.org

doi: 10.4103/2221-6189.390385 Impact Factor® 0.5

Risk factors for development of pneumothorax in patients with COVID−19 at a government health facility in North India: An exploratory case−control study

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ABSTRACT

Objective: To explore risk factors for the development of pneumothorax in patients with COVID-19 during the second COVID-19 wave at a northern Indian level 2 health facility.

Methods: Patients suffering from SARS-CoV-2 infection during the second wave of the COVID-19 pandemic in India (January -June 2021) at a tertiary care teaching hospital and level 2 COVID care facility were included. Cases who suffered from SARS-CoV-2 infection but did not develop pneumothorax were selected as matched controls. All details regarding demographics, clinical presentation, treatment, and outcome were recorded in a semi-structured proforma.

Results: Eleven patients with COVID-19 developed pneumothorax during the study period and 40 controls were included in the study. Five cases were smokers in comparison to only two in the control group. Type 2 diabetes mellitus was the most common comorbidity among both groups. Median change in C-reactive protein overall for cases and controls were around +14.0 and −41.9 and was statistically significant.

Conclusions: Inflammatory markers like C-reactive protein have significant correlations with the development of pneumothorax in COVID-19-infected patients. There is no sex predisposition to develop pneumothorax among patients with COVID-19.

KEYWORDS: COVID-19; Pneumothorax; Chest tube; Correlates; Risk factors; Inflammatory marker; C-reactive protein

1. Introduction

The second wave of COVID-19 in India is believed to have started in the early months of 2021 and the country was hit hard during its peak where around 400 000 new cases were recorded every day. It seemed to overwhelm the health systems in many places in the country. It reached its peak very quickly and this time the severity of the disease seemed to be very high in comparison to the first wave in mid to late 2020. It was probably because the absolute number of cases in the second wave was high, more patients with moderate

Significance

COVID-19 is a new disease condition with complications like pneumothorax and its risk factors are not well established. This study tries to identify the risk factors for development of pneumothorax among COVID-19 patients. Inflammatory markers like C-reaction protein have significant correlations with development of pneumothorax and that there is no sex predisposition to develop pneumothorax among patients with COVID-19.

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How to cite this article: Baidya M, Pandey SK, Solanki HK, Singh AD, Giri S, Altamash S. Risk factors for development of pneumothorax in patients with COVID-19 at a government health facility in North India: An exploratory case-control study. J Acute Dis 2023; 12(6): 238-243.

Article history: Received 16 July 2023; Revision 21 August 2023; Accepted 14 November 2023; Available online 12 December 2023

to severe disease required hospitalization and oxygen in a narrow period in comparison to the first wave of COVID-19 in the country. As a result, the number of ICU admissions increased abruptly and saturated the health system in the second wave, and along with it the reported cases of pneumothorax among these patients also increased. SARS-CoV-2 infection primarily affects the lung ranging from minor infections to severe acute respiratory distress syndrome[1-3]. Autopsy of COVID-19 patients revealed desquamation of pneumocytes, hyaline membrane deposition, and pulmonary edema suggesting features of acute respiratory distress syndrome. One of the complications of COVID-19 noted during the first wave was the development of spontaneous pneumothorax. Spontaneous pneumothorax can be primary or secondary. Primary spontaneous pneumothorax occurs in those who do not have any prior lung pathology whereas in secondary spontaneous pneumothorax, the patient had some form of prior lung pathology. Acute respiratory distress syndrome causing pneumothorax can be due to increased alveolar pressure, an increased negative pressure of the pleural cavity, shear stress, and changes in lung structure[4]. In the second wave of COVID-19 pandemic our institute encountered comparatively more cases of spontaneous pneumothorax compared to the first wave. More and more sick patients got admitted and almost every patient needed some sort of oxygen therapy. Along with it there was a rise in a number of spontaneous pneumothorax cases too. Therefore, this exploratory case-control study was planned to evaluate whether there are any contributory risk factors for the development of pneumothorax in patients with COVID-19.

2. Patients and methods

This is a record-based case-control study conducted at a tertiary care teaching hospital and Level 2 (L2) COVID-19 care facility in the western Uttar Pradesh, Delhi NCR region. The study was carried out from May 2021 to November 2021.

2.1. Inclusion and exclusion criteria

This study included all adult patients suffering from SARS-CoV-2 infection during the second wave of the COVID-19 pandemic in India (January-June 2021) and developing pneumothorax during treatment.

For each case, four cases who suffered from SARS-CoV-2 infection but did not develop pneumothorax were selected as matched controls. Cases and controls were comparable in age, sex, severity of disease, and date of admission.

Patients with a prior diagnosis of pneumothorax or a chest tube in situ were excluded from the study. Patients who had a previous history of spontaneous pneumothorax were also excluded from the study.

2.2. Data collection

To identify cases and suitable controls, all files of COVID-19 patients during the second wave of COVID-19 pandemic were retrieved from the medical record section. Four controls were intended to be included for each case to maximize the power of the study as the number of cases was relatively small. However, we could not find more than 40 matched controls for the 11 cases we had with pneumothorax at the study health facility. All the details like demographics, clinical presentation, treatment, and outcome were collected and recorded in a semi-structured proforma.

2.3. Ethical statement

This study was approved by the institutional ethics committee registered as GIMS IEC_ECR/1224/Inst./UP2019 with the number GIMS/IEC/HR/2022/13 dated on 30 April 2022.

2.4. Statistical analysis

Data analysis was done using SPSS software version 27[5] and the results were presented in form of frequencies and percentages. Chi square test or fisher exact test was applied for dichotomous variables. For continuous variables, t test was used for normally distributed variables; Mann Whitney U test was applied for normally distributed variables. P value of less than 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

A total of 11 patients with COVID-19 developed pneumothorax during their course of treatment at the study institute from 1st January 2021 to 30th June 2021 (6 males and 5 females). The mean age was (61.0±6.5) years in the case group. A total of 24 male and 16 female were randomly selected as controls with a mean age of (63.0±6.6) years. More than 45% of the cases were smoker while only 5% in the control group. Breathlessness was the most common symptom for both case and control groups followed by fever. Surprisingly only two patients (18.1%) from the case group and 20 patients (50%) from the control group had cough at the time of presentation. Type 2 diabetes mellitus was the most common comorbidity among both the groups followed by hypertension (Table 1).

Table 1. Socio-demographic and clinical characteristics (*n*, %).

Variable	Cases (*n*=11)	Control (*n*=40)
Sex		
Male	6 (54)	24 (60)
Female	5 (46)	16 (40)
Smoking		
Yes	5 (46)	2 (5)
No	6 (55)	38 (95)
Chief complaints		
Difficulty in breathing	11 (100)	33 (66)
Running nose	0 (0)	1 (3)
Dry cough	2 (18)	20 (50)
Chest pain	1 (9)	2 (5)
Generalized weakness	1 (9)	0 (0)
Vomiting	0 (0)	2 (5)
Fever	4 (36)	22 (55)
Co–morbidities		
Coronary artery disease	1 (9)	1 (3)
COPD	1 (9)	0 (0)
Diabetes	4 (36)	23 (58)
Hypertension	2 (18)	20 (50)
Hypothyroidism	1 (9)	8 (20)
Tuberculosis	1 (9)	0 (0)

Smoking: smoke for four or more days a week; COPD: chronic obstructive pulmonary disease.

3.2. Clinical parameters

The mean duration of symptoms onset before presentation and the mean oxygen saturation (SpO_2) were similar between two groups (P>0.05). There was no significant difference in the case number using treatment modalities like convalescent plasma and intravenous remdesivir drug between the two groups. Approximately 70% of patients in both groups received mechanical ventilation. Five out of 11 patients recovered in the case group, while 13 out of 40 recovered in the control group (Table 2).

3.3. Laboratory results

Changes in C-reactive protein (CRP), was significantly different between the two groups (P<0.05) (Table 3).

4. Discussion

Our study derived that the changes in the value of CRP was significant between the case and control groups. Various studies have suggested that COVID-19 causes a hyperimmune response in the body resulting in a cytokine storm[6-8]. In the case group in our study CRP increased till the development of pneumothorax whereas in the control group, there was a decline in these values. The mean haemoglobin (Hb) values in the case group also dropped from 13.2 g/dL to 12.3 g/dL at the time of development of pneumothorax but in the control group, there was an increase in the mean Hb from 12.7 g/dL to 13.1 g/dL. But the change in Hb values was not found to be significant. Probably the ongoing persistent inflammatory process along with the fall in the Hb has a contributory role in the development of pneumothorax.

Multicentric randomized control trials have revealed that the incidence of pneumothorax in patients with mechanical ventilation was 13%-15%[9,10]. We found no preponderance in sex and the mean age was above 60 years. In the case group, 64% of the patients suffered from one or more co-morbidities like hypertension, diabetes, hypothyroidism, coronary artery disease, tuberculosis, and asthma. In the control group, 80% of the patients suffered from one or more co-morbidities. In our study, we did not find any statistically significant association between any co-morbidity and pneumothorax,

Table 2. Clinical variables.

Variables	Cases (*n*=11)	Control (*n*=40)	*t*/*U*/χ^2	*P*
Duration before presentation (days, mean±SD)	4.5±2.7	4.5±2.7	0.001	0.919
SpO_2 (%, mean±SD)	81.70±10.25	81.50±10.93	0.228	0.946
Oxygen support mode (*n*, %)				
Nasal prong/NRBM/room air	3 (27.3)	13 (32.5)	0.109	0.741
NIV/Ventilator	8 (72.7)	27 (67.5)		
Fresh frozen plasma transfusion (*n*, %)				
Yes	6 (54.5)	14 (35.0)	0.684	0.408
No	5 (45.5)	26 (65.0)		
Remdesivir given before pneumothorax (*n*, %)				
Yes	7 (63.6)	14 (35.0)	1.858	0.173
No	4 (36.4)	26 (65.0)		
Hospital stay duration (days, median, Q1, Q3)	27.0 (40.0-9.0)	9.0 (12.0-5.0)	8.091	0.004
Outcome of patient (*n*, %)				
Recovered	5 (45.5)	13 (32.5)	0.194	0.660
Death	6 (54.5)	27 (67.5)		

GCS: Glasgow coma scale; NRBM: non-rebreathing mask; NIV: noninvasive ventilation.

Table 3. Change in selected laboratory parameters over time in cases and controls (median, Q1, Q3).

Variables	Cases (*n*=11)	Control (*n*=40)	*U*	*P*
CRP (mg/dL)				
At admission	73.9 (24.0, 139.0)	109.5 (81.8, 139.3)	2.251	0.134
At event	109 (62.8, 147.6)	60.6 (31.0, 95.5)	5.353	0.021
Change	14.0 (–2.4, +67.0)	–41.9 (–68.0, –7.0)	9.701	0.002
Hemoglobin (g/dL)				
At admission	13.4 (11.8, 13.6)	12.8 (11.0, 14.5)	0.278	0.598
At event	12.4 (10.8, 13.6)	13.1 (11.7, 14.4)	1.365	0.243
Change	–0.7 (–2.3, +1.0)	0.0 (–0.75, +1.30)	2.841	0.092
LDH (IU/L)				
At admission	753 (633, 1033)	1106.5 (753, 1493)	1.365	0.052
At event	881 (672, 1120)	1105.0 (633, 1511)	2.841	0.308
Change	56 (–134, +237)	–81.5 (–262.1, +176.0)	1.365	0.303
TLC (cells/ mL)				
At admission	11000 (8095, 18000)	12000 (9250, 15150)	0.047	0.828
At event	17000 (13900, 19200)	15000 (12150, 16750)	0.971	0.325
Change	3000 (–800, +6405)	3000 (–700, +6250)	0.016	0.900
Platelet count (10^5/mL)				
At admission	1.76 (1.55, 2.12)	1.65 (1.28, 2.42)	0.001	0.972
At event	2.8 (2.62, 3.42)	2.15 (1.45, 2.90)	2.253	0.133
Change	0.8 (0.06, 1.42)	0.4 (–0.16, +1.22)	2.116	0.146

LDH: lactate dehydrogenase , CRP: C-reactive protein, TLC: total leucocyte count.

but some studies have shown that diabetes and hypertension are most commonly associated with pneumothorax[11,12].

Patients were treated as per the protocol of our institute according to their disease severity. Some randomized control trials found that remdesivir can be effective, could reduce hospital stay, incidence of mechanical ventilation and oxygen requirement, and improve early recovery even possible survival benefits[13,14]. We found out that these therapies had no significant association with development of pneumothorax.

Martinelli *et al*. reported that only 1% of cases of COVID 19 developed pneumothorax[15]. They also reported that patient's survival after developing pneumothorax was lower in patients with intubation in comparison to those without intubation. In our study 5 (45.45%) out of 11 patients with pneumothorax survived, among whom two patients received non-invasive ventilation while only 13 patients with non-invasive ventilation survived in the case group. A study performed by Rizer *et al.* concluded that there was a significant decrease in 90-day survival post-chest tube insertion in comparison to those who did not have insertion (52% *vs*. 69%). They also reported long hospital stay and ICU stay post-chest tube insertion[16]. In our study, there was a beneficial effect of chest tube insertion on survival.

Barotrauma due to mechanical ventilation has been the foremost cause of development of pneumothorax[17-19]. Yang *et al*. observed that in China out of 37 critically ill patients infected with COVID-19 with mechanical ventilation only one patient developed pneumothorax[20]. Increased alveolar pressure in the diseased and inflamed lung is more prone to rupture. Along with inflamed lungs due to the infection, higher positive end-expiratory pressure was one of the risk factors in the development of pneumothorax[19]. Nalewajska *et al.* reported that 3 of their patients without lung pathology developed pneumothorax when put on a high-flow nasal cannula[21]. In a single-centre observational study done by Belletti *et al.* in Italy, they found only the duration from onset of symptoms to intubation and total bilirubin as independent risk factors for the development of pneumothorax[18].

Zantah *et al.* suggested that in COVID-19 patients cough could suggest the development of pneumothorax[22]. They reported that 4 out of 6 patients had cough as a predominant symptom. However, in our study, we found that only 2 patients out of 11 who developed pneumothorax had a cough at the time of presentation whereas 20 patients out of 40 in the control group had cough as the predominant symptom. In our study, we also found that 5 patients out of 11 patients in the case group had a history of smoking in comparison to 2/40 in the control group and the difference was statistically significant. So, we inferred that cough alone is not essentially associated with development of pneumothorax but smoking may be an associated risk factor.

Small sample size is the limitation of the study. Studies with larger sample sizes are needed in further study.

Our study shows that an increase in inflammatory markers like CRP had a significant correlation with the development of pneumothorax in COVID-19 patients. We did not find any significant correlation between sex, common co-morbidities and pneumothorax; while there is a positive correlation between smoking and development of pneumothorax.

Conflict of interest statement

The authors report no conflict of interest.

Funding

This study received no extramural funding.

Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

MB, SKP, ADS, SG, and SA were involved in data collection and compilation. MB, HKS, and SKP did data and statistical analysis. Manuscript preparation was done by MB and HKS. All authors reviewed and approved the final version of the manuscript.

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