

Pulmonary Barotrauma in COVID-19 Patients: Invasive versus Noninvasive Positive Pressure Ventilation

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Purpose: This study aims to determine the incidence and outcome of COVID-19 patients who required positive pressure ventilation (PPV) and subsequently developed pulmonary barotrauma (PBT). Also, to investigate the risk factors and predictors of these complications to better understand the disease pathogenesis.

Patients and Methods: This retrospective analysis enrolled all adult COVID-19 patients admitted through the period from October 1, 2020, to December 31, 2020. All patients who received any form of PPV were included. Patients were then divided into two groups based on PBT development, including subcutaneous emphysema, pneumothorax, and pneumomediastinum. Medical records of all patients were reviewed. Patients' demographics, laboratory data on admission, respiratory support modes, surgical interventions, and outcomes were collected and analyzed.

Results: In the specified period, 1095 patients were hospitalized due to COVID-19 illness. A total of 239 (21.8%) of all admitted patients received PPV. PBT accounted for 21.3% (51/239) of the study cohort. While both groups were equally exposed to the same modes of PPV, receiving invasive ventilation significantly correlated with decreased PBT odds (OR = 0.891; 95% CI, 0.803–0.988; $p=0.029$). PBT patients were significantly younger ($p<0.001$). Diabetes mellitus was found to have a protective effect on developing PBT (OR = 0.867; 95% CI, 0.782–0.962), while PO_2/FIO_2 ratio was inversely associated with higher odds of developing PBT in both univariate and multivariate analyses ($p=0.03$ and $p=0.019$, respectively).

Conclusion: COVID-19-infected patients are at a higher risk of developing PBT. Invasive positive pressure ventilation was associated with less PBT compared to noninvasive ventilation and delaying intubation does not seem to reduce the risk of pulmonary barotrauma.

Keywords: COVID-19, pulmonary barotrauma, pneumothorax, pneumomediastinum, positive pressure ventilation, adult respiratory distress syndrome

Introduction

In late December 2019, mysterious reported cases of “unknown pneumonia” were noticed in Wuhan, China.¹ It was found to be caused by a novel coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).¹ SARS-CoV-2 belongs to the beta-coronavirus family, which includes the virus responsible for Severe Acute Respiratory Syndromes (SARS) and Middle East Respiratory Syndromes (MERS) (SARS-CoV and MERS-CoV, respectively).^{1,2} SARS-CoV-2 appears to share the same human cell receptors as SARS-CoV,^{1,2}

which appear to cause multiple systems infection in some animals and mainly respiratory tract infections in humans, such as SARS and MERS.^{3,4} While most COVID-19-infected patients will have no or mild symptoms, few might progress to severe pneumonia, Acute respiratory distress syndrome (ARDS), or multiple organ failure.⁵ Hypoxemic respiratory failure and ARDS associated with COVID-19 has a variable case fatality rate (2–13%), with a mortality rate reaching up to 15% in cases requiring mechanical ventilation.^{6–8} Both pneumothorax (PNX) and pneumomediastinum (PMD) are known complications of mechanical ventilation.^{4,9} Retrospective studies of patients with COVID-19 have suggested that pneumothorax might occur in 1% of those requiring hospital admission, 2% of patients requiring intensive care unit (ICU) admission, and 1% of patients dying from the infection.^{5,9,10} More recently, 15% of ventilated patients developed pulmonary barotrauma (PBT), including subcutaneous emphysema, PNX, and PMD.¹¹

To our knowledge, the current literature describing subcutaneous emphysema, PNX, and PMD related to COVID-19 infection consists primarily of case series and single case reports. This observational case–control study describes subcutaneous emphysema, PNX, and PMD complications in patients with COVID-19 disease who required positive pressure ventilation (PPV). The aim is to determine these patients' incidence and outcome and investigate the risk factors and predictors of these complications to understand better the disease pathogenesis leading to these complications.

Patients and Methods

Study Design and Setting

This study is a single-center observational case–control study conducted at King Abdullah University Hospital (KAUH), the main tertiary hospital serving the north of Jordan. The hospital serves a population exceeding 2 million. Ethical approval was obtained from the Institutional Review Board (IRB) of the hospital, committed to the scientific research policy at Jordan University of Science and Technology (JUST) and KAUH. The ethics committee approved a waiver of consent from individual patients due to the study's retrospective nature. All the data was anonymized. Patients' confidentiality was protected following Declaration of Helsinki provisions.

Inclusion Criteria and Ventilation Protocol

All adult patients (age ≥ 18) who were tested positive for COVID-19 infection by Polymerase Chain Reaction (PCR) nasal swab test and were admitted to the hospital wards and critical care units due to COVID-19 complications through the period from October 1, 2020, to December 31, 2020, were enrolled. All patients who developed any element of PBT (PNX, PMD, or subcutaneous emphysema) and those who received any form of PPV either by using Non-Invasive Positive Pressure Ventilation (NIPPV) such as continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) and those who required Invasive positive pressure Ventilation (IPPV), were included.

All patients requiring IPPV were managed according to lung-protective ventilation strategies using low tidal volume (V_t) between 4 and 8 mL/kg predicted body weight, using a volume-limited assist control mode and initial Positive End Expiratory Pressure (PEEP) of 5 cm H₂O and titrate up gradually to improve oxygenation while targeting plateau pressure (P_{plat}) of <30 cm H₂O to limit lung injury. All IPPV and patients requiring higher oxygen requirements while on NIPPV were transferred to a critical care unit for close monitoring. Only patients requiring intermittent NIPPV were kept on the floor or intermediate care units according to their clinical condition and their oxygen and pressure support requirements. Except for honoring patients' refusal to receive IPPV, all patients were considered for IPPV support when indicated regardless of their underlying comorbidities. According to our hospital sedation and muscle relaxant protocol, sedation medications used in patients with ARDS included benzodiazepines such as Lorazepam (1–10 mg/hour) or Midazolam (2–10 mg/hour) infusions in combination with a potent analgesic such as Fentanyl, Remifentanyl, or Morphine. Muscle relaxants if needed were only used in addition to sedation and analgesics infusions to ensure patient synchronization with the ventilator. This sedation protocol applies to patients receiving IPPV. On the other hand, patients receiving NIPPV, the use of sedatives or analgesics were avoided and were only given minimum doses as needed basis for comfort.

Procedure

Clinical and laboratory data were collected retrospectively by reviewing the medical records of the patients. Age, sex,

body mass index (BMI), smoking history, chronic medical illnesses, and history of underlying lung disease, presenting symptoms, laboratory values on admission, respiratory support modes, ventilator settings at the time of the barotrauma event, surgical interventions, and outcomes (death or discharge) were collected. All data were collected according to a standardized protocol to minimize recorder bias. Imaging was reviewed for all patients throughout their admission. PBT was radiologically identified at the time of the event by the ordering physician and consulted pulmonologist with the confirmation of a radiologist. All Chest X-Rays and reports were reviewed by both the thoracic surgeon and pulmonologist study authors while collecting the study data.

Data Analysis

All patients who received any form of PPV were divided into two groups, the first group is the group of patients who developed any form of PBT, and the second (control) group consists of all patients who did not develop PBT (NPBT). We used frequencies and percentages to represent patients' distribution across categories and means/medians for continuous variables with standard deviations and ranges as spread measures. Chi-square test was used to compare frequencies and Fisher's exact test in case of low cell counts. The Student's *t*-test was used for differences between means, and the Wilcoxon rank-sum test in cases of variables that lacked a normal distribution was examined by visual histograms and confirmed by the Shapiro-Wilk test. All tests were two-tailed, and a *p*-value of less than 0.05 was considered statistically significant. Odds ratios were calculated as an effect measure to compare the odds of having PBT. Additionally, a multiple regression model was calculated to predict PBT using independent variables including mode of ventilation, age, comorbidities such as hypertension, diabetes mellitus (DM), chronic kidney disease, laboratory measurements such as ferritin, urea, lactate dehydrogenase, D-dimer, platelet, neutrophil and lymphocyte counts, X-ray findings (unilateral/bilateral), and respiratory parameters including PCO₂, and PO₂/FIO₂ ratio. All statistical analyses were done using R statistical language (version 4.0.4).¹²

Results

Sample Characteristics

A total of 1095 patients were diagnosed and hospitalized with COVID-19 during the study period. Two hundred and

thirty-nine (21.8%) of all admitted patients received PPV during their hospital stay and were divided into two groups. The first group (PBT group) included 51 (21.3%) patients who developed elements of PBT (PNX, PMD, or subcutaneous emphysema) after receiving any form of PPV. The second group (NPBT group) consisted of 188 (78.7%) patients who also received any form of PPV but did not develop PBT. Out of 239 patients who received PPV, 112 patients received IPPV (47%), 17 patients developed PBT. On the other hand, 127 patients received NIPPV (53%). Out of those who received NIPPV, 60 patients received BiPAP, and 67 patients received CPAP, out of which 15 and 19 patients developed PBT, respectively (Figure 1). The mean age of patients was 66.1 (\pm 13.6) years, 61.1% of patients were males, 35.1% of them were smokers, and mean body mass index (BMI) was 30.2 (\pm 6.93). Shortness of breath was the most common presenting symptom (83.7%), followed by dry cough (71.5%) and fever (68.2%). Out of 239 patients, 165 had hypertension (69.0%), 119 had DM (49.8%), 53 had ischemic heart disease (22.2%), and other patients had heart failure, chronic kidney disease, active malignancy, chronic

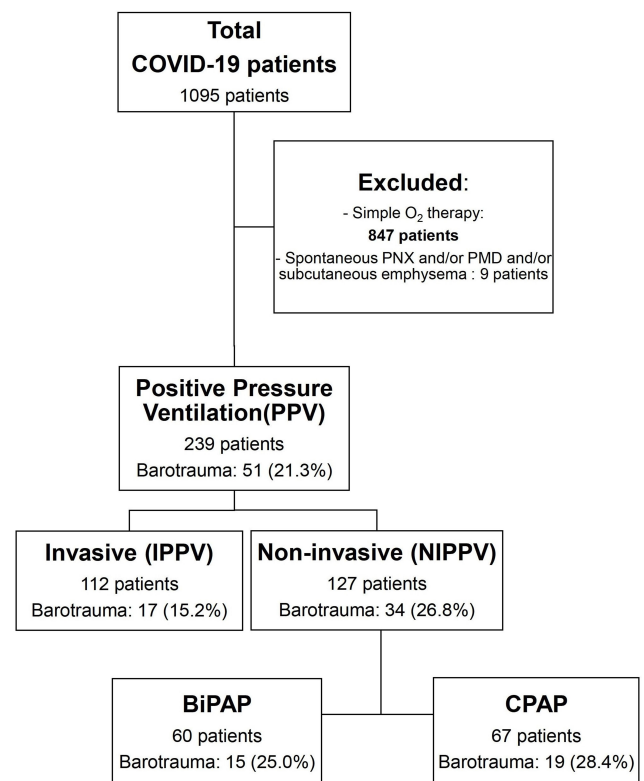


Figure 1 Flow chart demonstrating the distribution of patients, inclusion and exclusion, and ventilation.

Abbreviations: PNX, pneumothorax; PMD, pneumomediastinum; BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure.

obstructive pulmonary disease (COPD), and asthma (Table 1). The overall mortality rate of 1095 admitted COVID-19 patients was 21.1%. The mortality rate of patients who received either forms of PPV was 87.9%, which is higher than of patients who did not receive PPV (2.6%). The highest mortality rate from COVID-19 infection was found among patients who developed PBT (90.2%). The mean length of hospital stay was 13 days (\pm 8.73 days). When comparing both groups, patients who developed PBT-related complications were significantly younger, with a mean age difference of 6.9 years ($p=0.002$) (Figure 2). The male-female ratio was about 1:1, with no difference in mean body mass index (BMI) between the two groups. About 38.3% of the NPBT group were smokers, while 23.5% of those who developed PBT were smokers ($p=0.069$). We found no difference in the frequencies of presenting symptoms. NPBT group had higher

rates of comorbidities such as hypertension (72.3% vs 56.9%, $p=0.041$), DM (54.3% vs 33.3%, $p=0.012$), and chronic kidney disease (16.0% vs 5.9%, $p=0.045$). No difference in mortality was observed between PBT and NPBT groups ($p=0.739$). A sub-analysis of the patients' characteristics who received IPPV vs NIPPV was performed (Table 2). Patients who received NIPPV are significantly younger ($p=0.046$), and the death rate in patients receiving IPPV is higher ($p < 0.001$). Other findings showed no clinically significant difference in the patients' demographics, explaining the lower barotrauma rate in the IPPV group.

Laboratory Results

As described in Table 3. NPBT group had high mean serum urea level (mean difference = 2.94 mmol/L, $p=0.009$) and higher serum creatinine levels (mean

Table 1 Patients' Demographics

Patients' Characteristics	Barotrauma (N=51)	No Barotrauma (N=188)	P-value	Overall (N=239)
Age	60.7 (15.9)	67.6 (12.6)	0.002	66.1 (13.6)
Gender				
Female	22 (43.1%)	71 (37.8%)	0.592	93 (38.9%)
Male	29 (56.9%)	117 (62.2%)		146 (61.1%)
BMI	30.5 (7.20)	30.0 (6.78)	0.616	30.2 (6.93)
Smoking	12 (23.5%)	72 (38.3%)	0.069	84 (35.1%)
Presenting symptoms				
Shortness of breath	42 (82.4%)	158 (84.0%)	0.939	200 (83.7%)
Dry cough	37 (72.5%)	134 (71.3%)	0.997	171 (71.5%)
Fever	36 (70.6%)	127 (67.6%)	0.846	163 (68.2%)
Length of stay (days)	13.7 (8.93)	12.8 (8.69)	0.457	13.0 (8.73)
Comorbidities				
Hypertension	29 (56.9%)	136 (72.3%)	0.051	165 (69.0%)
Diabetes mellitus	17 (33.3%)	102 (54.3%)	0.012	119 (49.8%)
Ischemic heart disease	10 (19.6%)	43 (22.9%)	0.758	53 (22.2%)
Heart failure	5 (9.8%)	29 (15.4%)	0.428	34 (14.2%)
Chronic kidney disease	3 (5.9%)	30 (16.0%)	0.070	33 (13.8%)
Asthma	0 (0%)	5 (2.7%)	NA	5 (2.1%)
COPD	0 (0%)	5 (2.7%)	NA	5 (2.1%)
Malignancy	4 (7.8%)	14 (7.4%)	1.000	18 (7.5%)
Outcome				
Dead	46 (90.2%)	164 (87.2%)	0.739	210 (87.9%)
Discharged home	5 (9.8%)	24 (12.8%)		29 (12.1%)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

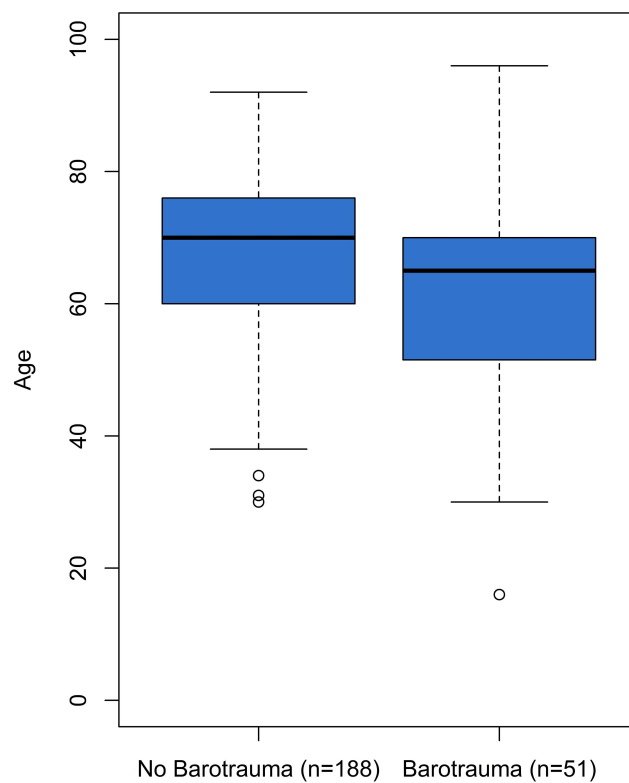


Figure 2 Side-by-side box of age for the two groups.

difference = 56.1 $\mu\text{g/dl}$, $p < 0.001$) than PBT patients. On the other hand, PBT group had higher levels of ferritin (mean difference = 118 ng/mL , $p=0.07$), but using Wilcoxon median test yields a significant difference in ferritin medians, $p\text{-value}=0.019$, lactate dehydrogenase levels (mean difference = 180 U/L , $p=0.013$), D-dimer levels (mean difference = 1.49, $p=0.05$) and higher white blood cell count (mean difference = $1.8 \times 10^3 /\mu\text{L}$, $p=0.038$) than the control group. There was no difference in neutrophils, lymphocytes, platelets, and blood levels of hemoglobin, C-reactive protein, creatinine kinase, and troponin between the two groups (Table 3). Nonetheless, using Wilcoxon median test, a significant difference in medians in neutrophils count was detected in the PBT group ($p\text{-value}=0.024$).

Barotrauma and Mechanical Ventilation

Out of a total of 51 patients who experienced PBT, 17 patients had PBT while receiving IPPV support, while 19 patients were on CPAP support, and 15 were on BiPAP support (Figure 1). PBT manifested as PNX, PMD, or subcutaneous emphysema, as one or combination of more than one. A total of 23 patients of the PBT group

manifested as PNX (45.1%), 25 patients developed PMD (49.0%), and 23 patients developed subcutaneous emphysema (45.1%) (Figure 3). The timeline of events for individuals who experienced PBT is illustrated in Figure 4.

Most PBT patients were treated with a chest tube (76.5%), with a drain size of either 24 or 28 French (Fr). The insertion site was in the right, left, or bilateral for 16, 12, and 10 patients, respectively (Table 4).

Although both groups were exposed to the same PPV modes, receiving IPPV therapy was significantly correlated with decreased PBT odds (OR = 0.891; 95% CI, 0.803–0.988; $p=0.029$). Interestingly, NIPPV caused more PBT (34/51, 56%) than IPPV (17/51, 33.3%). Out of a total of 112 patients who required IPPV, 17 patients developed PBT (33.3%), while 27% (34/127) of patients who required NIPPV support, either BiPAP or CPAP, developed PBT (Table 5). The duration between the time of admission to the PPV support was not significantly different between the two groups. There was no difference in the mean tidal volume/ideal body weight, but the mean respiratory rate was higher in the NPBT group (1.8 breaths per minute, $p=0.01$), and although $\text{PaO}_2/\text{FIO}_2$ was significantly low in both groups, it was significantly lower in the PBT group (mean difference = 17.7, $p=0.002$). There was no difference in PCO_2 ($p=0.13$). There was no significant difference or effect seen in the inspiratory positive airway pressure (IPAP), pressure support, positive end-expiratory pressure (PEEP), or fraction of inspired O_2 on PBT development.

Radiological Findings

We have evaluated chest X-Ray findings for all PBT patients. Thirty-eight patients (74.5%) had bilateral lung involvement with diffuse infiltrates, 7 (13.7%) patients had left lung involvement, and 6 (11.8%) patients had right lung involvement. Chest tubes were inserted in the same side of the infiltrate in 4/10 patients, while on the opposite involvement side in 6/10 patients. For patients with bilateral infiltrates findings, chest tubes were inserted in the right side for nine patients, in the left side for nine patients, and bilaterally in 9 patients (Table 6). The location of X-ray findings was distributed equally in pneumomediastinum and subcutaneous emphysema patients, but pneumothorax patients had more tendency to be shown on the left ($p=0.023$).

Predictors of Barotrauma

Logistic regression was carried out on variables that had a notable difference between PBT and NPBT patients, in

Table 2 Patients' Demographics; Invasive Positive Pressure Ventilation vs Non-Invasive Positive Pressure Ventilation

Patients' Characteristics	Non-Invasive (N=127)	Invasive (N=112)	P-value	Overall (N=239)
Age	64.7 (12.8)	67.7 (14.4)	0.046	66.1 (13.6)
Gender				
Female	49 (38.6%)	44 (39.3%)	1.000	93 (38.9%)
Male	78 (61.4%)	68 (60.7%)		146 (61.1%)
BMI	31.0 (7.40)	29.2 (6.18)	0.216	30.2 (6.93)
Smoking	44 (34.6%)	40 (35.7%)	1.000	84 (35.1%)
Length of stay (days)	13.4 (9.63)	12.7 (7.62)	0.911	13.0 (8.73)
Presenting symptoms				
Fever	85 (66.9%)	78 (69.6%)	0.824	163 (68.2%)
Shortness of breath	105 (82.7%)	95 (84.8%)	0.785	200 (83.7%)
Dry cough	95 (74.8%)	76 (67.9%)	0.296	171 (71.5%)
Comorbidities				
Hypertension	88 (69.3%)	77 (68.8%)	1.000	165 (69.0%)
Diabetes mellitus	59 (46.5%)	60 (53.6%)	0.363	119 (49.8%)
ISCHEMIC heart disease	26 (20.5%)	27 (24.1%)	0.604	53 (22.2%)
Heart failure	17 (13.4%)	17 (15.2%)	0.833	34 (14.2%)
Chronic kidney disease	18 (14.2%)	15 (13.4%)	1.000	33 (13.8%)
Asthma	2 (1.6%)	3 (2.7%)	0.667	5 (2.1%)
COPD	4 (3.1%)	1 (0.9%)	0.375	5 (2.1%)
Malignancy	12 (9.4%)	6 (5.4%)	0.342	18 (7.5%)
Outcome				
Dead	100 (78.7%)	110 (98.2%)	<0.001	210 (87.9%)
Discharged home	27 (21.3%)	2 (1.8%)		29 (12.1%)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

addition to variables that were considered clinically significant. A significant regression equation was found using 15 variables and 140 degrees of freedom ($p < 0.0001$), with an R^2 measure of 27.1% and an adjusted- R^2 measure of 19.3% (Table 7). In univariate analysis, PBT group patients were significantly younger ($p < 0.001$), and this effect remains in multivariate analysis ($p = 0.038$). DM was found to reduce the odds for developing PBT (OR = 0.867; 95% CI, 0.782–0.962). This effect persisted even after adjusting for age and other possible predictors in multivariate analysis (OR = 0.839; 95% CI, 0.725–0.970). While chronic kidney disease showed a significant effect in univariate analysis using chi-square test (p -value=0.045) but did not have significant effect in multivariate analyses, hypertension had an effect in the univariate analysis only (OR = 0.886; 95% CIs, 0.791–0.991; $p = 0.034$). Lymphocyte count was found to have a significant effect in multivariate analysis ($p = 0.038$).

Other laboratory findings, including urea levels and lactate dehydrogenase, had significant adverse effects on PBT in univariate analysis but not in the multivariate analysis.

Other laboratory findings, including ferritin, D-dimer, platelet, and neutrophil counts, did not significantly predict PBT in either analysis. As for radiological findings, unilateral findings were significantly associated with PBT occurrence (OR=1.822; 95% CI, 1.274–2.606; $p = 0.003$), but we did not find any significance for it in multiple regression. Lower PO_2/FIO_2 was associated with higher odds of developing PBT in both univariate and multivariate analyses ($p = 0.03$ and $p = 0.019$, respectively). PCO_2 had no significant effects in either analysis. To further examine DM's protective effect, we ran an additional model that does not include the diabetes variable. R^2 measure was reduced from 27.1% to 24.2% and adjusted- R^2 decreased from 19.3% to 16.3%. Finally, we compared this model against the original model using an ANOVA F-test, and it

Table 3 Laboratory Investigations and Results

Laboratory Investigation	Barotrauma (N=51)	No Barotrauma (N=188)	P-value	Overall (N=239)
C-reactive protein Mean (SD) Median [Min, Max]	165 (101) 143 [0.640, 373]	168 (95.9) 159 [5.30, 487]	0.747	167 (96.9) 156 [0.640, 487]
Creatinine Kinase Mean (SD) Median [Min, Max]	373 (950) 125 [18.0, 5970]	341 (753) 148 [14.0, 8120]	0.56	348 (799) 147 [14.0, 8120]
Ferritin Mean (SD) Median [Min, Max]	897 (559) 796 [60.0, 2000]	779 (692) 591 [24.0, 4760]	0.07	807 (663) 629 [24.0, 4760]
Urea (mmol/l) Mean (SD) Median [Min, Max]	9.46 (6.19) 8.00 [1.00, 32.0]	12.4 (8.04) 10.0 [2.60, 49.0]	0.009	11.7 (7.76) 9.50 [1.00, 49.0]
Serum Creatinine (µg/dl) Mean (SD) Median [Min, Max]	97.9 (56.7) 89.0 [2.00, 341]	154 (148) 110 [11.0, 1040]	<0.001	142 (136) 103 [2.00, 1040]
Lactate dehydrogenase Mean (SD) Median [Min, Max]	1250 (524) 1100 [384, 2990]	1070 (485) 931 [463, 3520]	0.013	1110 (498) 971 [384, 3520]
Troponin Mean (SD) Median [Min, Max]	0.0719 (0.157) 0.0195 [0.00300, 1.00]	0.0590 (0.141) 0.0200 [0.00270, 1.46]	0.795	0.0623 (0.145) 0.0200 [0.00270, 1.46]
White blood cells Mean (SD) Median [Min, Max]	12.0 (7.36) 11.0 [1.90, 48.0]	10.2 (6.11) 9.00 [0, 49.0]	0.038	10.6 (6.42) 9.69 [0, 49.0]
Hemoglobin (g/dl) Mean (SD) Median [Min, Max]	12.5 (2.40) 13.0 [2.40, 15.9]	12.1 (2.31) 12.4 [0, 17.6]	0.097	12.2 (2.33) 12.5 [0, 17.6]
Platelet Mean (SD) Median [Min, Max]	227 (88.3) 225 [2.70, 479]	235 (107) 213 [0, 722]	0.738	233 (103) 215 [0, 722]
Neutrophil count Mean (SD) Median [Min, Max]	9810 (5260) 9310 [13.7, 26,300]	8690 (5210) 7820 [0, 30,900]	0.064	8930 (5230) 8080 [0, 30,900]
Lymphocyte count Mean (SD) Median [Min, Max]	1630 (6100) 725 [3.99, 44,200]	1040 (1660) 720 [0, 17,200]	0.948	1170 (3170) 720 [0, 44,200]
D-dimer Mean (SD) Median [Min, Max]	5.07 (6.24) 2.06 [0.480, 20.0]	3.58 (5.19) 1.68 [0.270, 20.0]	0.05	3.95 (5.49) 1.70 [0.270, 20.0]

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum.

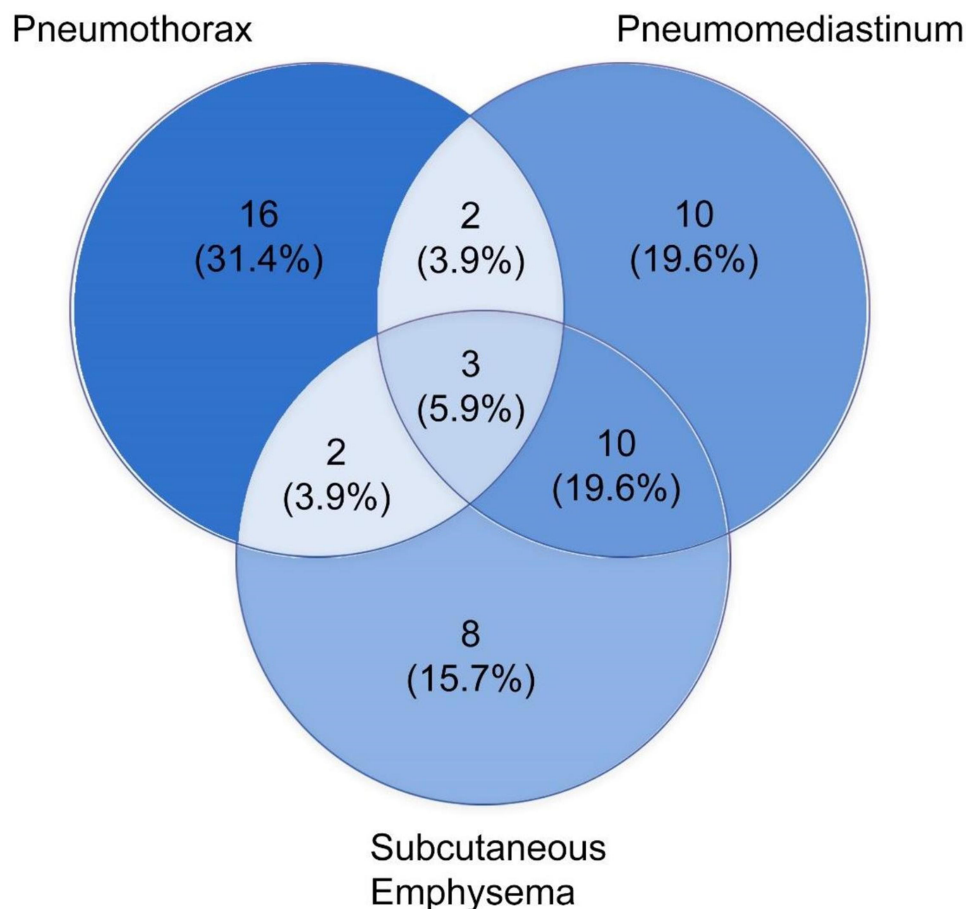


Figure 3 Venn diagram showing distribution of patients having different scenarios of barotrauma.

showed a significant difference ($F = 5.70$; $p=0.018$). Predictors of barotrauma are demonstrated in Figure 5.

Discussion

This observational study reports PBT in 60 patients out of 1095 SARS-CoV-2 infected hospitalized adults during the study period. To our knowledge, this is the largest study population of PBT in SARS-CoV-2 infection from a single center and one of few to describe associated risk factors in these patients. The overall incidence of PBT in our study of the SARS-CoV-2 population was about 5.5%. Most of the affected patients (85%) developed PBT while receiving PPV support, an incidence of 21.3%. A total of 9 cases developed spontaneous PNx, PMD, or subcutaneous emphysema out of 856 of SARS-CoV-2 admitted patients who did not require any form of PPV with an overall incidence of 1.0%. Multiple studies have reported PNx in association with COVID-19 pneumonia. The most extensive published retrospective case series included 71 patients with PBT from 16 centers by

Martinelli et al reported incidence of about 25% of intubated patients developed PNx or PMD,¹³ which is similar to the incidence observed in our cohort. On the other hand, multiple case series studies reported a 10–14% incidence of PBT in mechanically ventilated ARDS patients infected with COVID-19.^{11,14–16}

In our study, the incidence of PBT was higher in patients who received NIPPV than IPPV (34/127,26.8% vs 17/112,15.2%, respectively, $p=0.043$). More patients from PBT group received NIPPV than IPPV (66.7% and 33.3%, respectively), compared to the NPBT group (50.5% and 49.5%, respectively). Our study is the largest and the second to report a higher incidence of PNx in patients who received NIPPV in comparison to IPPV support. Jones et al reported Seven out of eight patients (87.5%) in the barotrauma group had received NIPPV as the initial mode of advanced respiratory support, compared with 27 of 75 (36.0%) in the non-barotrauma group ($p=0.007$).¹⁷ Applying the universally accepted ARDS Network guidelines to ventilate ARDS patients using

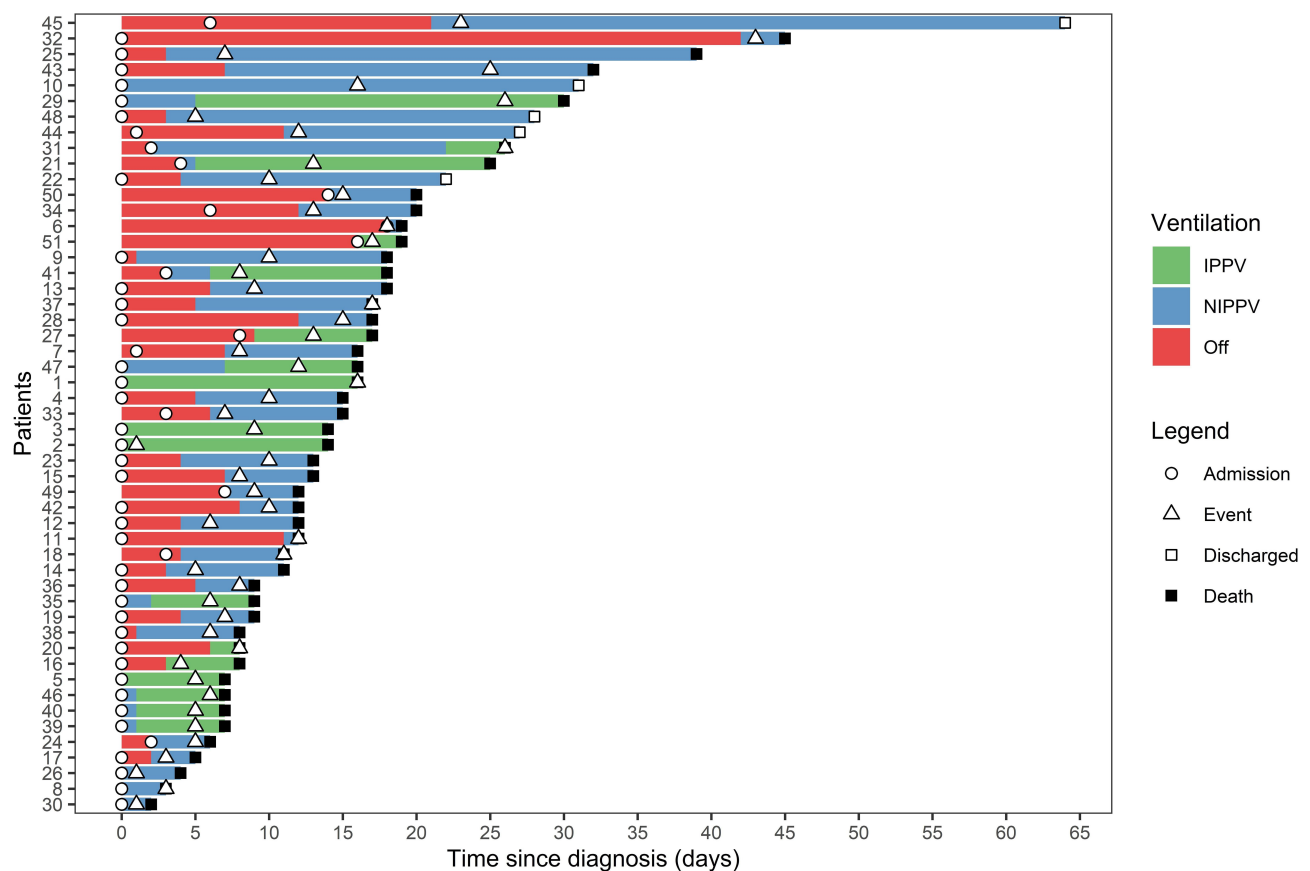


Figure 4 Swimmer's plot showing individual timelines of events for patients who experienced barotrauma. The start of each bar represents the day of diagnosis with COVID-19 (day 0), and the end represents the outcome, whether death or discharge. Each circle represents day of hospital admission, the cross mark represents day of ventilation, the triangle mark represents day of barotrauma event. Finally, white square represents day of discharge, and black square represents day of death. Bars representing time before diagnosis in days before ventilation therapy are shown in red, in green during invasive positive pressure ventilation (IPPV) therapy and shown in blue for patients who underwent non-invasive positive pressure ventilation (NIPPV) therapy.

a protective-ventilation approach based on reducing the tidal volume to about $6 \text{ mL} \cdot \text{kg}^{-1}$ of ideal body weight and maintaining the airway plateau pressure below $30 \text{ cmH}_2\text{O}$ has helped to reduce the incidence of PBT significantly.^{18–20} Rates of NIPPV-associated barotrauma are not known but are reportedly rare in COVID-19 related ARDS.^{17,21,22} However, in NIPPV, the tidal volumes and transpulmonary pressure are dependent on the patient's spontaneous respiratory effort, which may result in highly variable and fluctuant transpulmonary pressures that cannot be limited or controlled,^{23,24} which may result in self-inflicted PBT in patients with ARDS. Higher incidence of PBT in NIPPV might be also attributed to the limited use of sedation and muscle relaxant in NIPPV group compared to IPPV which might have impacted patient-ventilator desynchrony, and subsequently higher risk of developing PBT. This supports the importance of maintaining patient-ventilator synchrony to lower the risk of PBT. There is no agreement on using CPAP and NIPPV in severe COVID-

19,²⁵ but it has been promoted in some guidelines.^{26,27} Belletti et al evaluated predictors of PNx/PMD in mechanically ventilated COVID-19 patients and concluded that delayed intubation was an independent predictor of PNx/PMD development.²⁸ In that study, the group who developed PBT had a longer time from symptoms onset to intubation than the group who did not develop PBT (13 vs 10 days, $p=0.004$). This higher incidence of PBT in NIPPV, as well as the reported cases of spontaneous PNx, may support that the underlying cause of PNx/PMD is due to an underlying virus-induced mechanism as part of the natural course/sequela of the SARS-CoV-2 disease rather than a mechanical PPV-induced complication caused by high transpulmonary pressure. This theory is also supported by the observation of overall higher incidence of PNx/PMD in COVID-19 related ARDS in comparison to non-COVID-19 ARDS. Lemmers et al observed a seven-fold increase in PBT in COVID-19 ARDS with a PMD incidence of 13% in COVID-19

Table 4 Pulmonary Barotrauma Group; Mode of Ventilation, Complication, and Management

Barotrauma Patients	(N=51)
Mode of ventilation	
NIPPV	34 (66.7%)
BiPAP	15 (29.4%)
CPAP	19 (37.3%)
IPPV	17 (33.3%)
Barotrauma manifestation	
Pneumothorax	23 (45.1%)
Pneumomediastinum	25 (49.0%)
Subcutaneous emphysema	23 (45.1%)
Day of event after diagnosis	
Mean (SD)	9.33 (5.57)
Median [Min, Max]	8.00 [1.00, 26.0]
Day of PPV after admission	
Mean (SD)	5.10 (7.07)
Median [Min, Max]	3.00 [0, 44.0]
Day of event after PPV	
Mean (SD)	4.20 (4.45)
Median [Min, Max]	3.00 [1.00, 20.0]
Need for chest tube	39 (76.5%)
Chest tube size (Fr)	
24	15 (29.4%)
28	29 (56.9%)
Insertion Site	
Right	16 (31.4%)
Left	12 (23.5%)
Bilateral	10 (19.6%)
Observation	13 (25.5%)

Abbreviations: NIPPV, non-invasive positive pressure ventilation; CPAP, continuous positive airway pressure; BiPAP, bi-level positive airway pressure; IPPV, invasive positive pressure ventilation; PPV, positive pressure ventilation; SD, standard deviation; Min, minimum; Max, maximum; Fr, French gauge.

ARDS versus 1.9% in non-COVID-19 ARDS.¹⁴ The reported incidence of PNx/PMD in non-COVID-19 ARDS is ranging between 3% and 15%.^{29–32} Spontaneous pneumothorax was also reported as a complication of the SARS caused by SARS-CoV-1 with an incidence of 1.7% in hospitalized patients.³³

Many clinical and laboratory variables have been investigated in our cohort, looking for predictors associated with a higher risk of developing PBT in patients receiving PPV. Interestingly, the group who developed PBT were younger and with fewer comorbidities. Except for the higher prevalence of DM and better PO₂/FIO₂ ratio observed in the NPBT group, there was no significant

difference observed in the other factors between the two groups to predict the risk of developing PBT in patients receiving PPV. A lower PO₂/FIO₂ ratio usually indicates a greater extent of lung injury or ARDS, thus raising the risk of PNx/PMD. Many studies have well-described DM as a risk factor for developing severe pneumonia in COVID-19-infected patients.^{34–38} Patients with type 2 DM were more likely to develop complications, more intensive care unit admissions, and death from COVID-19.

On the other hand, in an observational study from France, 1317 patients with DM were hospitalized with COVID-19. Neither long-term glycemic control nor routine therapies were associated with COVID-19 severity, intubation, and death.³⁹ Up to our knowledge, no studies to date have described the effect of pre-existing DM in developing PBT in patients with SARS-CoV-2 infection. A meta-analysis study done by Ji et al looking into the effect of DM on the risk and mortality of acute lung injury/ARDS reviewed 14 studies and found no effect of having a pre-existing DM on the risk and mortality of ALI/ARDS.⁴⁰ DM may play an essential role in the immune system and, consequently, contribute to a reduced overall inflammatory response with the attenuation of cytokine release and the reduction of neutrophil migration.^{41,42} This blunted inflammatory response might help reduce the rate of inflammation associated with SARS-CoV-2 infection. The mechanism is yet to be explained, but this may add on to the support of a possible immunomodulated response on the pathogenesis of developing PNx/PMD in patients infected with SARS-CoV-2.

The laboratory findings indicated significantly higher levels of urea and creatinine in the NPBT group. This finding can be explained by the higher incidence of chronic kidney disease compared to PBT group (16% vs 5.9%, respectively). Additionally, although not statistically significant, the smoking rate in the PBT group seems to be less than the NPBT group (23.5% vs 38.3%, respectively). Smoking is usually associated with chronic obstructive pulmonary disease (COPD)/emphysema which places patients at a higher risk of PNx while on PPV. Tindle et al described that nicotine and cigarette smoke have been reported to decrease levels of angiotensin-converting enzyme 2 (ACEII).⁴³ Moreover, it may modulate COVID-19 disease severity through the cholinergic anti-inflammatory pathway, inhibiting macrophage-driven hyper-inflammation and platelet reactivity, thus reducing

Table 5 Comparison Between Pulmonary Barotrauma and Control Group Ventilation Modes and Settings

Positive Pressure Ventilation (PPV)	Barotrauma (N=51)	No Barotrauma (N=188)	P-value	Overall (N=239)
Mode of ventilation				
IPPV	17 (33.3%)	95 (50.5%)	0.043	112 (46.9%)
NIPPV	34 (66.7%)	93 (49.5%)		127 (53.1%)
Day of PPV after admission				
Mean (SD)	5.10 (7.07)	4.33 (5.16)	0.787	4.49 (5.61)
Median [Min, Max]	3.00 [0, 44.0]	3.00 [0, 44.0]		3.00 [0, 44.0]
O ₂ therapy 24h before event				
IPPV	17 (33.3%)	95 (50.5%)	0.043	112 (46.9%)
NIPPV	34 (66.7%)	93 (49.5%)		127 (53.1%)
Tidal Volume/ideal body weight (mL/kg)				
Mean (SD)	6.6 (0.7)	6.3 (0.4)	0.48	6.4 (0.5)
Median [Min, Max]	6.9 [6.2, 7.5]	6.4 [5.6, 7.9]		6.5 [5.6, 7.9]
Respiratory Rate				
Mean (SD)	17.9 (2.83)	19.7 (3.54)	0.01	19.4 (3.48)
Median [Min, Max]	18.0 [10.0, 24.0]	20.0 [10.0, 28.0]		20.0 [10.0, 28.0]
Inspiratory Positive Airway Pressure (IPAP)				
Mean (SD)	22.1 (4.10)	22.5 (4.20)	0.755	22.4 (4.14)
Median [Min, Max]	20.0 [16.0, 32.0]	22.0 [13.0, 30.0]		22.0 [13.0, 32.0]
Pressure Support				
Mean (SD)	15.4 (3.47)	15.8 (3.54)	0.336	15.7 (3.52)
Median [Min, Max]	15.0 [8.00, 25.0]	15.0 [7.00, 25.0]		15.0 [7.00, 25.0]
Positive End Expiratory Pressure (PEEP)				
Mean (SD)	8.75 (3.63)	9.43 (3.49)	0.198	9.28 (3.53)
Median [Min, Max]	8.00 [0, 15.0]	10.0 [0, 16.0]		10.0 [0, 16.0]
Fraction of Inspired O ₂ (FIO ₂)				
Mean (SD)	95.5 (14.7)	92.5 (15.8)	0.121	93.2 (15.6)
Median [Min, Max]	100 [8.00, 100]	100 [28.0, 100]		100 [8.00, 100]
Chest X-Ray				
Bilateral	38 (74.5%)	184 (97.9%)	<0.0001	222 (92.8%)
Unilateral	13 (25.5%)	1 (0.5%)		14 (7.2%)
Partial pressure of carbon dioxide (PCO ₂)				
Mean (SD)	35.3 (7.35)	38.6 (12.4)	0.13	37.9 (11.5)
Median [Min, Max]	34.0 [23.0, 53.0]	36.0 [20.0, 116]		35.0 [20.0, 116]
PO ₂ /FIO ₂				
Mean (SD)	67.5 (45.5)	85.2 (50.8)	0.002	81.4 (50.1)
Median [Min, Max]	58.0 [19.5, 317]	66.0 [10.0, 350]		63.5 [10.0, 350]

Abbreviations: IPPV, invasive positive pressure ventilation; NIPPV, non-invasive positive pressure ventilation; SD, standard deviation; Min, minimum; Max, maximum; PO₂/FIO₂, arterial partial pressure of oxygen to fraction of inspired oxygen.

the cellular injury and severity of the disease.⁴³ Nevertheless, it is suggested that smoking may confer some protective effect against the development of COVID-19 infection but might be associated with worse disease outcome once acquired.⁴⁴

Chest radiograph of most SARS-CoV-2 patients who required PPV revealed diffuse lung involvement with equal bilateral infiltrates distribution. Most patients had diffuse and equally distributed bilateral infiltrates (38/51, 74.5%). Out of patients who developed PBT, 13 had

Table 6 Chest X-Ray Findings and Their Relation to the Pulmonary Barotrauma

Chest X-Ray Findings	Right (N=6)	Left (N=7)	Bilateral (N=38)	P-value	Overall (N=51)
Insertion site					
Right	2 (33.3%)	5 (71.4%)	9 (23.7%)	NA	16 (31.4%)
Left	1 (16.7%)	2 (28.6%)	9 (23.7%)		12 (23.5%)
Bilateral	1 (16.7%)	0 (0%)	9 (23.7%)		10 (19.6%)
Observation	2 (33.3%)	0 (0%)	11 (28.9%)		13 (25.5%)
Pneumothorax	3 (50.0%)	7 (100%)	13 (34.2%)	0.591	23 (45.1%)
Pneumomediastinum	2 (33.3%)	2 (28.6%)	21 (55.3%)	0.094	25 (49.0%)
Subcutaneous emphysema	3 (50.0%)	1 (14.3%)	19 (50.0%)	<0.001	23 (45.1%)

a preferential unilateral lung involvement with one side involved with more infiltrates than the other; the chest tube was placed more in the opposite to the side with worse

infiltrates (7/13, 54%) than of the same side (3/13, 23%). No apparent reason to explain this observation in our study. An assumption is that the lung areas with more

Table 7 Logistic Regression Analysis of the Predictors of Barotrauma

Predictors of Barotrauma	Univariate		Multivariate	
	Coefficients	P-value	Coefficients	P-value
Age	-0.00623	<0.001	-0.00529	0.038
Mode of ventilation [Invasive]	OR = 0.891 (95% CI, 0.803–0.988)	0.029	OR = 0.876 (95% CI, 0.768–0.999)	0.049
Diabetes mellitus (Yes)	OR = 0.867 (95% CI, 0.782–0.962)	0.007	OR = 0.839 (95% CI, 0.725–0.970)	0.018
Hypertension (Yes)	OR = 0.886 (95% CI, 0.791–0.991)	0.034	OR = 1.025 (95% CI, 0.882–1.190)	0.750
Chronic kidney disease (Yes)	OR = 0.868 (95% CI, 0.746–1.009)	0.045	OR = 0.946 (95% CI, 0.760–1.178)	0.618
Ferritin	0.00005	0.297	0.00008	0.177
Urea	-0.0082	0.018	-0.0026	0.638
LDH	0.000127	0.039	0.00001	0.855
D-dimer	0.0093	0.104	0.00597	0.362
Neutrophil count	0.000007	0.175	0.00001	0.103
Lymphocyte count	0.00001	0.241	0.00002	0.038
Platelet count	-0.00012	0.637	-0.00054	0.106
Chest X-Ray findings (Unilateral)	OR = 1.822 (95% CI, 1.274–2.606)	0.003	OR = 1.462 (95% CI, 0.924–2.314)	0.104
PCO ₂	-0.0042	0.071	-0.0044	0.099
PO ₂ /FIO ₂	-0.0012	0.03	-0.0018	0.019

Abbreviations: LDH, lactate dehydrogenase; Pco₂, partial pressure of carbon dioxide; PO₂/FIO₂, arterial partial pressure of oxygen to fraction of inspired oxygen.

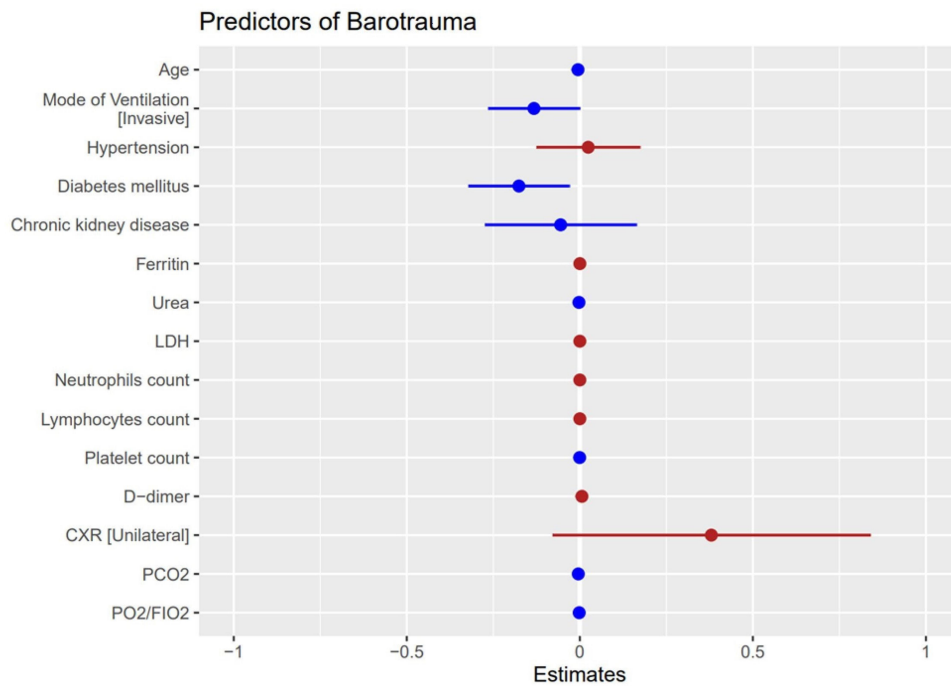


Figure 5 Forest plot representing coefficients of predictors via a multiple regression model, dots in red are harmful predictors, and dots in blue are protective predictors of barotrauma. Lines for each variable represent 95% confidence intervals.

Abbreviations: LDH, lactate dehydrogenase; CXR, Chest X-Ray; PCO₂, partial pressure of carbon dioxide; PO₂/FIO₂, arterial partial pressure of oxygen to fraction of inspired oxygen.

infiltrates are stiffer and probably more resistant to developing PBT than areas with less infiltrate involvement. One important finding is that the tendency to follow conservative measures rather than proceeding with interventional measures and chest tube insertion was much more in patients with bilateral infiltrates (11/38, 29%) than with preferential infiltrates (2/13, 15%).

The mean time to develop PBT in our cohort was about nine days from diagnosis and about four days after the placement on any form of PPV. This finding is similar to the study by Edwards et al in which PNx/PMD occurred in less than four days from the start of mechanical ventilation.¹⁶ Multiple studies indicated that PNx usually develops at a relatively late stage (3–8 weeks) after the onset of symptoms.^{45,46} In a study by Capaccione et al, the time from intubation to PNx event was 14.9 days which is similar to that described by Belletti et al, in which the time from intubation to PNx was 14 days.^{15,28} Most patients who developed PBT in our study died (88%). The occurrence of PBT did not change the overall outcome of our study population. Multiple studies reported PBT to attribute to increased mortality in patients with COVID-19 infection, whether spontaneous or iatrogenic, due to PPV, both invasive and noninvasive.^{47,48} The mortality rate

reported by Belletti et al was 61% in patients who developed PNx/PMD, higher than those who did not have PNx/PMD (39%, $p=0.04$).²⁸ Abdallat et al described a case series of 25 patients with COVID-19 infection who developed PBT with a mortality rate of 64%.⁴⁹ Martinelli et al indicated that although post-PNx survival was lower in patients receiving IPPV than patients who were not intubated, no significant difference was found between patients receiving IPPV or those not receiving IPPV ventilation. That led to a conclusion that COVID-19 infection-related PNx did not seem to be an independent marker of poor prognosis,^{13,50} which is similar to our study. Multiple factors are thought to be contributing to the high overall mortality rate of SARS-CoV-2 patients in our cohort. First, the higher degree of severity in the patients and the hospital's nature as the primary referral center accepts more severe cases with a more complicated course or advanced disease stage and frequently with significant comorbidities. The other main contributing factor is the overwhelmingly large number of admitted and accumulated patients in a short time frame with limited human resources and strict technical availability.

Our study has involved a relatively large number of patients reported in a single tertiary center. Nonetheless,

our finding has its limitations that include the following: First, being a single-center observation, this will restrict the generalization of the results and findings. Secondly, our protocol in managing SARS-CoV-2 patients in our hospital does not include a computer tomography (CT) investigation. The absence of the CT from the investigation protocol may result in underestimating the barotrauma cases, especially mild pneumomediastinum or anterior pneumothoraxes that are not clinically apparent or difficult to be seen on the chest radiograph; moreover, the presence of necrotizing infections that may predispose for PNx is underestimated.

Conclusion

Our cohort study results highlighted and supported that COVID-19 ARDS infected patients are at a higher risk of developing PBT than non-COVID-19 ARDS. There is an added risk of developing PBT in patients receiving NIPPV compared to IPPV and avoiding intubation does not seem to reduce the risk of PBT and PNx/PMD development. These findings are essential to consider when placing a management protocol of COVID-19 ARDS.

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Institutional Review Board (IRB) of the hospital, committed to the scientific research policy at Jordan University of Science and Technology (JUST) and KAUH. This study was conducted following the 1975 Helsinki declaration, as revised in 2008 and its later amendments or comparable ethical standards.

Consent for Publication

The ethics committee approved a waiver of consent from individual patients due to the study's retrospective nature.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no conflicts of interest and no financial disclosures.

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