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Cardiothoracic Imaging

Barotrauma in COVID 19: Incidence, pathophysiology, and effect on prognosis

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ABSTRACT

Objectives: To investigate the incidence, risk factors, and outcomes of barotrauma (pneumomediastinum and subcutaneous emphysema) in mechanically ventilated COVID-19 patients. To describe the chest radiography patterns of barotrauma and understand the development in relation to mechanical ventilation and patient mortality.
Methods: We performed a retrospective study of 363 patients with COVID-19 from March 1 to April 8, 2020. Primary outcomes were pneumomediastinum or subcutaneous emphysema with or without pneumothorax, pneumoperitoneum, or pneumoretroperitoneum. The secondary outcomes were length of intubation and death. In patients with pneumomediastinum and/or subcutaneous emphysema, we conducted an imaging review to determine the timeline of barotrauma development.
Results: Forty three out of 363 (12%) patients developed barotrauma radiographically. The median time to development of either pneumomediastinum or subcutaneous emphysema was 2 days (IQR 1.0–4.5) after intubation and the median time to pneumothorax was 7 days (IQR 2.0–10.0). The overall incidence of pneumothorax was 28/363 (8%) with an incidence of 17/43 (40%) in the barotrauma cohort and 11/320 (3%) in those without barotrauma ($p \leq 0.001$). In total, 257/363 (71%) patients died with an increase in mortality in those with barotrauma 33/43 (77%) vs. 224/320 (70%). When adjusting for covariates, barotrauma was associated with increased odds of death (OR 2.99, 95% CI 1.25–7.17).
Conclusion: Barotrauma is a frequent complication of mechanically ventilated COVID-19 patients. In comparison to intubated COVID-19 patients without barotrauma, there is a higher rate of pneumothorax and an increased risk of death.

1. Introduction

The Coronavirus disease (COVID-19) global pandemic has contributed to over 5.2 million deaths worldwide.[1,2] The reported mortality rates of intubated COVID-19 patients ranges from 66 to 97%[3,4] and mechanical ventilation is associated with an increased risk of death in these critically ill patients.[3–5] Barotrauma, including pneumo-mediastinum, subcutaneous emphysema, pneumoretroperitoneum, pneumoperitoneum, and pneumothorax are known complications of mechanical ventilation.[6] Although there is a paucity of literature describing barotrauma in COVID-19 patients, the reported barotrauma rate (15%) is higher than the non COVID-19 mechanically ventilated population.[7] Similar rates (25%) have been reported in severe acute respiratory syndrome (SARS-COV-1)[8] of 25% and from 10 to 67% in the acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) literature.[9–12] Furthermore, cases of COVID-19 with associated

spontaneous pneumomediastinum, subcutaneous emphysema, and pneumothorax in the non-intubated population have recently been described in the literature.[13–16] These studies suggest that underlying decreased lung compliance may place these patients at an increased risk for these complications. Similar findings in SARS-COV-1 and ARDS have led authors to question whether these findings may be associated with increasing disease severity and poorer outcomes.[14,16]

The risk factors associated with barotrauma have not been evaluated in the COVID-19 population. We investigate these features, describe the radiographic patterns of barotrauma, and delineate the timeline of development in relation to mechanical ventilation and the relationship to patient mortality.

2. Methods

2.1. Patient selection

This multi-center retrospective study was approved by our institutional review board. Written informed consent was waived.

Using an institutionally compiled COVID-19 dataset, we identified 367 patients over the age of 18 with reverse transcription polymerase chain reaction (RT-PCR) confirmed COVID-19 who were intubated for at least two days from March 1 to April 8, 2020 in three hospital centers within the Mount Sinai Health System in New York City. Using the mPower ™ (Nuance, Burlington, Massachusetts, United States) search and analytics platform, radiology information system (RIS) data were extracted for each patient and the initial chest radiograph on the day of intubation was identified for review. Patients with findings consistent with air leak on initial imaging were excluded ($N = 4$). After this exclusion, 363 patients were included for analysis. Based on the provided intubation date, subsequent chest radiograph reports were extracted for each patient and were reviewed to identify the primary outcomes of interest. Each patient was followed to discharge. The earliest intubation period was 3/3/2020 and the last discharge date was 7/9/2020 covering the study period. A total of 2178 chest radiographs were reviewed.

The primary outcomes of interest were pneumomediastinum or subcutaneous emphysema with or without pneumothorax, pneumoperitoneum, or pneumoretroperitoneum. The secondary outcomes of interest were length of intubation and death.

The radiology reports were manually reviewed for any mention of pneumomediastinum or subcutaneous emphysema and 43/363 (12%) patients with at least one of these findings were identified. An image review of all radiographs ($n = 419$) belonging to these patients was performed.

Clinically relevant variables obtained from the institutionally compiled COVID-19 dataset included age, sex, ethnicity, race, body mass index (BMI), asthma, chronic obstructive pulmonary disease (COPD), hypertension (HTN), diabetes, cancer, chronic kidney disease (CKD), heart failure, ARDS, and smoking history. Additional variables including length of intubation and ventilator settings (tidal volume, fraction of inspired oxygen (FiO$_2$), peak end expiratory pressure (PEEP), respiratory rate, plateau pressure) were obtained through chart review.

2.2. Image review

In the subset of 43 patients with pneumomediastinum and/or subcutaneous emphysema without preceding pneumothorax, we conducted an image review of all 419 radiographs to determine the timeline of pneumomediastinum development and resolution in relation to mechanical ventilation.

All chest radiographs were reviewed by a cardiothoracic radiologist with >10 years of experience and a cardiothoracic imaging fellow using a picture archiving and communication system (PACS) workstation. Radiographs were reviewed independently, and final decisions were reached by consensus. The readers were not blinded to the diagnosis of

COVID-19, however, they were blinded to the clinical report including the presence of pneumomediastinum, subcutaneous emphysema, and pneumothorax as well as the clinical characteristics of each case. For patients with identified barotrauma, radiographs both before and after the identified barotrauma were identified. The severity of disease on radiograph was rated utilizing an established rating system on a scale from 1 to 6.[17] All chest radiographs were performed portably with the patient in the anterior posterior (AP) projection in the emergency department or intensive care unit setting.

2.3. Imaging analysis

Each chest radiograph was analyzed for the presence of external catheters including endotracheal tube, tracheostomy tube, enteric tube, chest tube, and central venous catheters as well as pneumomediastinum, subcutaneous emphysema, pneumothorax, and intra-abdominal air (including pneumoretroperitoneum and/or pneumoperitoneum). Retroperitoneal air was identified radiographically as gas outlining the lateral liver, kidneys, stomach, and the paravertebral musculature while pneumoperitoneum was identified as air collecting beneath the diaphragm. For data analysis purposes, pneumoperitoneum and pneumoretroperitoneum were treated as a single variable. Lung parenchyma was simultaneously evaluated for the presence of pulmonary opacities as defined by the Berlin definition for ARDS.[18]

2.4. Statistical analysis

Bivariate analysis of continuous variables, such as BMI, was performed using the Kruskal-Wallis H Test. Bivariate analysis of categorical variables such as patient race, patient sex, smoking history, and comorbidities was performed utilizing chi-squared test. A multivariable logistic regression model adjusting for sociodemographic variables and comorbidities and including any barotrauma as an independent variable was performed for the outcome of death. In order to ensure usability of as many records as possible in multivariable analysis, missing BMI ($N = 37$, 10.2%) were imputed using predictive mean matching using models that included the outcomes of interest, demographic information, and clinical variables.[19] These values were then utilized in the multivariable model through multiple imputation according to Rubin's rules.[20] In analyzing the severity scores of chest radiographs performed prior to and after barotrauma, weighted Cohen's kappa coefficient was used to assess agreement in scoring between the two cardiothoracic radiologists. A paired t-test was performed to identify differences in severity prior to and after barotrauma. A p-value of <0.05 (two-tailed) was considered statistically significant. All analysis was completed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

A total of 363 mechanically ventilated COVID-19 patients met inclusion criteria, comprising 226 men (62%) and 137 women (38%) with a median age of 66 years [interquartile range (IQR) 57–75]. The most frequent comorbidities were obesity 153/363 (42%), HTN 122/363 (34%), and diabetes 97/363 (27%). Forty three out of 363 (12%) patients developed barotrauma during their mechanical ventilation as defined by pneumomediastinum or subcutaneous emphysema. One hundred and sixty one out of 363 (44%) patients had a clinical diagnosis of ARDS by Berlin criteria (17) with 23/161 (14.3%) developing barotrauma ($p = 0.26$). Patients who developed barotrauma were less likely to have HTN (3 (7%) vs 119 (37%), $p \leq 0.001$), diabetes [4 (10%) vs 93 (29%), $p \leq 0.01$], and chronic kidney disease [0 (0%) vs 39 (12%), $p = 0.03$]. There was no statistically significant difference in age, race, ethnicity, smoking history, asthma, COPD, BMI, or Angiotensin-converting enzyme (ACE) inhibitors or Angiotensin II receptor blocker

(ARB) use between those who developed barotrauma and those who did not (Table 1).

The overall incidence of pneumothorax was 28/363 (8%) with an incidence of 17/43 (40%) in the barotrauma cohort and 11/320 (3%) in those without barotrauma ($p \leq 0.001$). (Table 1) During the study period, 257/363 (71%) patients died with a non-significant increase in mortality in those with barotrauma 33/43 (77%) vs. 224/320 (70%) ($p = 0.46$). In the subset of patients who died ($n = 257$), there was a higher median age (70 [IQR 61–77] vs. 61 [IQR 50–68], $p < 0.001$) and patients were more likely to have HTN (97 (40%) vs. 25 (21%), $p < 0.001$), heart failure (26 (10%) vs. 4 (3%), $p = 0.03$) and chronic kidney disease (33 (14%) vs. 6 (5%), $p = 0.03$). There was no statistically significant difference in rates of smoking, asthma or COPD or BMI in those who died. When adjusting for clinical and sociodemographic covariates,

barotrauma was associated with increased odds of death (OR 2.99, 95% CI 1.25–7.17) (Table 2).

There were no statistically significant differences between ventilator settings (tidal volume, fraction of inspired oxygen (FiO_2), peak end expiratory pressure (PEEP) and plateau pressure) between the two cohorts (Table 1).

3.2. Image review results

419 chest radiographs belonging to the 43/363 (12%) patients with barotrauma were included in the image review. At the time of barotrauma development, all patients had bilateral pulmonary opacities on radiography. All patients with barotrauma developed both pneumomediastinum and subcutaneous emphysema. The median time from intubation to either pneumomediastinum or subcutaneous emphysema was 2 days (IQR 1.0–4.5).

Forty-one out of 43 (95%) patients demonstrated concurrent pneumomediastinum and subcutaneous emphysema or pneumomediastinum alone as the first abnormal collection of air visualized radiographically. The remaining two out of 43 (5%) patients had subcutaneous emphysema identified prior to pneumomediastinum but developed radiographic evidence of pneumomediastinum within 24 h. Seventeen out of 43 (40%) patients developed pneumothoraces with a median time from intubation to development of seven days (IQR 2.0–10.0). All patients who developed a pneumothorax had both pneumomediastinum and subcutaneous emphysema at the time of pneumothorax development. Seven out of 17 (41%) patients had bilateral pneumothoraces and 10/17 (59%) were unilateral (seven on the right and three on the left). No patients had a central venous catheter or nasogastric tube placed immediately prior to the development of a pneumothorax or subcutaneous emphysema. Eight out of 17 patients who developed a

Table 1
Patient characteristics of the barotrauma and no barotrauma groups.

	Overall	No barotrauma	Barotrauma	p-Value
Number of patients	363	320	43	
Age, median (IQR), years	66.00 [57.00, 75.00]	67.00 [58.00, 75.00]	63.00 [54.50, 70.50]	**0.04**
Age category (%)				0.10
(0,50)	43 (11.8)	35 (10.9)	8 (18.6)	
(50,65)	115 (31.7)	98 (30.6)	17 (39.5)	
(65,130)	205 (56.5)	187 (58.4)	18 (41.9)	
Sex (% female)	137 (37.7)	123 (38.4)	14 (32.6)	0.56
Ethnicity (%)				**0.003**
Non-Hispanic	201 (55.4)	185 (57.8)	16 (37.2)	
Hispanic	98 (27.0)	77 (24.1)	21 (48.8)	
Other/unknown	64 (17.6)	58 (18.1)	6 (14.0)	
Race (%)				0.12
White	77 (21.2)	69 (21.6)	8 (18.6)	
Asian	17 (4.7)	15 (4.7)	2 (4.7)	
Black	89 (24.5)	84 (26.2)	5 (11.6)	
Other/unknown	180 (49.6)	152 (47.5)	28 (65.1)	
BMI (median [IQR])	29.4 [25.8, 35.4]	29.31 [25.6, 35.7]	29.83 [25.9, 33.3]	0.87
BMI category (%)				0.70
Normal	67 (20.6)	61 (21.4)	6 (14.6)	
Overweight	106 (32.5)	90 (31.6)	16 (39.0)	
Obesity	107 (32.8)	94 (33.0)	13 (31.7)	
Severe obesity	46 (14.1)	40 (14.0)	6 (14.6)	
Asthma (%)	13 (3.6)	13 (4.1)	0 (0.0)	0.36
COPD (%)	10 (2.8)	10 (3.1)	0 (0.0)	0.50
Hypertension (%)	122 (33.6)	119 (37.2)	3 (7.0)	**<0.001**
Diabetes (%)	97 (26.7)	93 (29.1)	4 (9.3)	**0.01**
Cancer (%)	16 (4.4)	15 (4.7)	1 (2.3)	0.75
CKD (%)	39 (10.7)	39 (12.2)	0 (0.0)	**0.03**
CHF (%)	30 (8.3)	30 (9.4)	0 (0.0)	0.07
Smoking status (%)				**0.03**
Never	180 (49.6)	155 (48.4)	25 (58.1)	
Former/current	83 (22.9)	80 (25.0)	3 (7.0)	
Unknown	100 (27.5)	85 (26.6)	15 (34.9)	
Time to death, median (IQR), days	6 [2,13]	5 [1,12]	10 [6, 17]	**0.004**
Pneumothorax (%)	28 (7.7)	11 (3.4)	17 (39.5)	**<0.001**
Death (%)	257 (70.8)	224 (70.0)	33 (76.7)	0.46
ARDS (%)	161 (44.4)	138 (43.1)	23 (53.5)	0.26
Deceased (%)	257 (70.8)	224 (70.0)	33 (76.7)	0.46
TV (median [IQR])	450 [400, 480]	450 [400, 480]	430 [400, 468]	0.41
PEEP (median [IQR])	15 [10, 18]	15.00 [10.00, 18.00]	15.00 [13, 16]	0.62
PP (median [IQR])	28 [27, 32]	32 [30, 34]	26 [26, 26]	0.22
On Home ACE or ARB (%)	96 (26.4)	88 (27.5)	8 (18.6)	0.29

Abbreviations: IQR, interquartile range; BMI, body mass index; CKD, chronic kidney disease; CHF, congestive heart failure; ARDS, acute respiratory distress syndrome; TV, tidal volume; FiO_2, fraction of inspired oxygen; RR, respiratory rate; PEEP, peak end expiratory pressure; PP, plateau pressure.
Bold= P values <.01

Table 2
Adjusted odds ratios for death for intubated patients. Adjustment was made for age, sex, race, ethnicity, BMI, smoking status, comorbidities, and any barotrauma as listed in the table.

	Odds ratio	95% CI	P-value
Age category			
Age ≥21 years and <50 years	Reference	Reference	Reference
Age ≥50 years and <65 years	2.75	1.21–6.24	0.02
Age >65 years	7.34	3.13–17.22	< 0.001
Sex			
Male	Reference	Reference	Reference
Female	0.48	0.27–0.83	0.01
Race			
White	Reference	Reference	Reference
Black	1.07	0.47–2.45	0.87
Asian	0.64	0.16–2.65	0.54
Other/unknown	0.54	0.24–1.24	0.15
Ethnicity			
Non-Hispanic			
Hispanic	1.10	0.52–2.34	0.80
Other/unknown	1.24	0.58–2.65	0.58
BMI category, kg/m^2			
Normal, <25	Reference	Reference	Reference
Overweight	2.23	0.97–5.14	0.06
Obesity	1.74	0.78–3.89	0.18
Severe obesity	1.79	0.65–4.89	0.26
Smoking status			
Never	Reference	Reference	Reference
Former/current smoker	0.6	0.29–1.28	0.19
Unknown	0.83	0.45–1.51	0.53
Comorbidities			
Asthma	6.72	0.66–68.17	0.11
Chronic obstructive pulmonary disease	2.17	0.21–22.92	0.52
Hypertension	3.22	1.44–7.2	0.01
Diabetes	0.87	0.43–1.76	0.69
Chronic kidney disease	2.34	0.66–8.25	0.19
Heart failure	1.42	0.36–5.52	0.61
Cancer	0.85	0.2–3.58	0.82
Barotrauma	2.99	1.25–7.17	0.01

pneumothorax had a chest tube placed and one of the 17 developed tension morphology which ultimately resulted in death. Eleven out of 43 (26%) patients developed intraabdominal air (pneumoperitoneum or pneumoretroperitoneum) with a median time from intubation to development of 5 days (IQR 1.0–9.5). All patients with pneumoperitoneum or pneumoretroperitoneum had pneumomediastinum and subcutaneous emphysema prior to these findings and five out of 11 (45%) also had a pneumothorax prior to the dissection of air into the abdomen.

Twenty six of 43 (60%) patients died prior to the resolution of barotrauma. The barotrauma resolved in all remaining 16 patients with a median time to resolution of 5 days (IQR-2.3-9.5). Of these 16 patients, seven (44%) died after barotrauma resolution but prior to extubation, seven (44%) underwent tracheostomy placement, two (12%) were successfully extubated.

Agreement was substantial for both pre-barotrauma (Kappa 0.68) and post-barotrauma (Kappa 0.71). The post-barotrauma group had a higher severity score (mean 5.2, sd 0.81) compared to the pre-barotrauma group (5.0, sd 0.83) although this difference was not statistically significant ($p = 0.15$).

4. Discussion

Our study found a high incidence of barotrauma 43/363 (12%) in intubated patients with COVID-19 and demonstrates a pattern of development that is evaluable by radiography. Furthermore, our study found barotrauma was associated with an increased risk of death.

4.1. Incidence

The 12% incidence of barotrauma in mechanically ventilated patients with COVID-19 and 43% in patients with COVID-19 who met diagnostic criteria for ARDS concur with the incidence reported in similar COVID-19 populations.[7,21,22] In the medical literature, the incidence of barotrauma with mechanical ventilation varies with the underlying indication for assisted ventilation. The highest incidence is seen in patients with ARDS which prior to the use of lower tidal volumes and plateau pressures was estimated to be up to 76%[11,12] and with protective lung ventilation strategy is now estimated around 10%.[10]

4.2. Mechanism of development

In the cohort of patients who developed pneumomediastinum and subcutaneous emphysema, 41/43 (95%) demonstrated pneumomediastinum alone or concurrently with subcutaneous emphysema as the first abnormal collection of air visualized radiographically. Both pneumomediastinum and subcutaneous emphysema were identified at a median of two days post intubation with pneumothorax or intraabdominal air (pneumoperitoneum pneumoretroperitoneum) identified at a median of 7 days (IQR 2.0–10.0) and 5 days, respectively. The subsequent time interval of pneumothorax and intraabdominal air is consistent with the reported pattern described with pulmonary interstitial emphysema (PIE).[23,24] (Fig. 1) This mechanism described by Macklin et al. as occurring with increased intrathoracic pressure causing overinflation of alveoli without adequate expansion of the associated
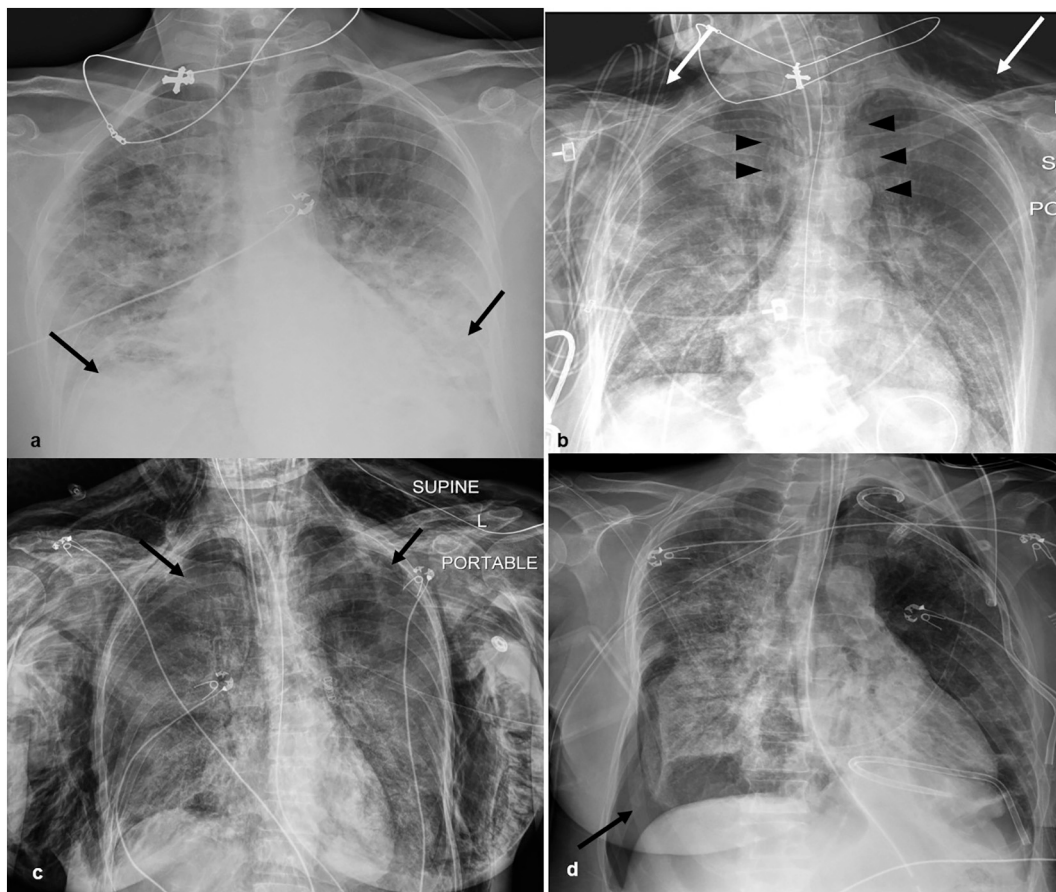

Fig. 1. Barotrauma over 39 days: 56 year old female with RT-PCR confirmed COVID-19 and a history of ulcerative colitis intubated 1 day post admission. a. Frontal chest radiograph on presentation demonstrates bilateral opacities (arrows) in a basilar predominant pattern, compatible with COVID-19 pneumonia. b. Pneumomediastinum (arrowheads) and subcutaneous emphysema (arrows) developed 2 day post intubation. c. New left and increasing right small pneumothoraces (arrows) 8 days post intubation resulting in right chest tube placement. d. Recurrent large right pneumothorax (arrow) 34 days post intubation with bilateral chest tubes in place. The patient died 5 days later (39 days after intubation) without resolution of barotrauma.

vessel. This pressure gradient from the alveolus to the vascular sheath results in alveolar rupture and dissection of air into the bronchovascular sheath. Air then dissects into the mediastinum, pleural space, subcutaneous tissues, and retroperitoneum.[23,25] Air travels into the retroperitoneum via the fascial planes surrounding the aorta and esophagus. Pneumoperitoneum is likely due to air dissecting along the aorta and the mesenteric branches into the bowel subserosa with subsequent rupture into the peritoneum.[26] Identification of subcutaneous emphysema and pneumomediastinum on radiography may be one of the few objective signs of significant alveolar rupture and PIE development.

Of note, two of the 43 (5%) patients in the barotrauma cohort had subcutaneous emphysema identified radiographically prior to pneumomediastinum but developed radiographic evidence of pneumomediastinum within 24 h. These patients likely had pneumomediastinum that was radiographically occult or temporarily resolved. Therefore, identifying subcutaneous emphysema on radiography prior to pneumomediastinum (and in the absence of an alternative explanation such as placement of a new central venous catheter) is compatible with the pathophysiology outlined by Macklin.

There is a complex relationship between ventilation parameters and barotrauma development in the mechanically ventilated patient and even when following lung protective strategies, barotrauma in COVID-19 may still occur.[27] Most studies reveal that PEEP is not associated with an increased incidence of barotrauma and demonstrates a significant increase in the incidence of barotrauma with increasing plateau pressures.[28–32] Overall, our results did not demonstrate a statistically

significant link between barotrauma and ventilatory pressures and volumes. Our results are similar to reports in the pulmonary ARDS literature[10] and those assessing barotrauma in mechanically ventilated COVID-19 patients who were treated with lung protective protocols.[27]

4.3. Imaging features

Pneumomediastinum is recognized on chest radiography as curvilinear or linear lucencies surrounding mediastinal structures. The radiographic signs of barotrauma include signs of pneumomediastinum: the continuous diaphragm sign, the tubular artery sign, and signs of pneumothorax such as the deep sulcus sign (Fig. 2).[33] The continuous diaphragm sign is identified by air tracking continuously beneath the heart and is suggestive of pneumomediastinum or rarely pneumopericardium. The tubular artery sign demonstrates air outlining the branches of the aorta, which is best appreciated on cross sectional imaging. The deep sulcus sign suggests pneumothorax on supine imaging as air collects anteriorly and basally, in contrast to an upright radiograph where air collects at the lung apices. Radiographically, PIE manifests as interstitial cystic or linear lucencies extending from the hilum, which are best appreciated on cross sectional imaging.[34] (Fig. 3) Pneumomediastinum is often a subtle finding, but as our results demonstrate, it is often associated with subcutaneous emphysema and places the patient at an increased risk for pneumothorax and death. Therefore, when subcutaneous emphysema is identified on radiography, the mediastinum and pleural spaces should be scrutinized for air. Additionally, in
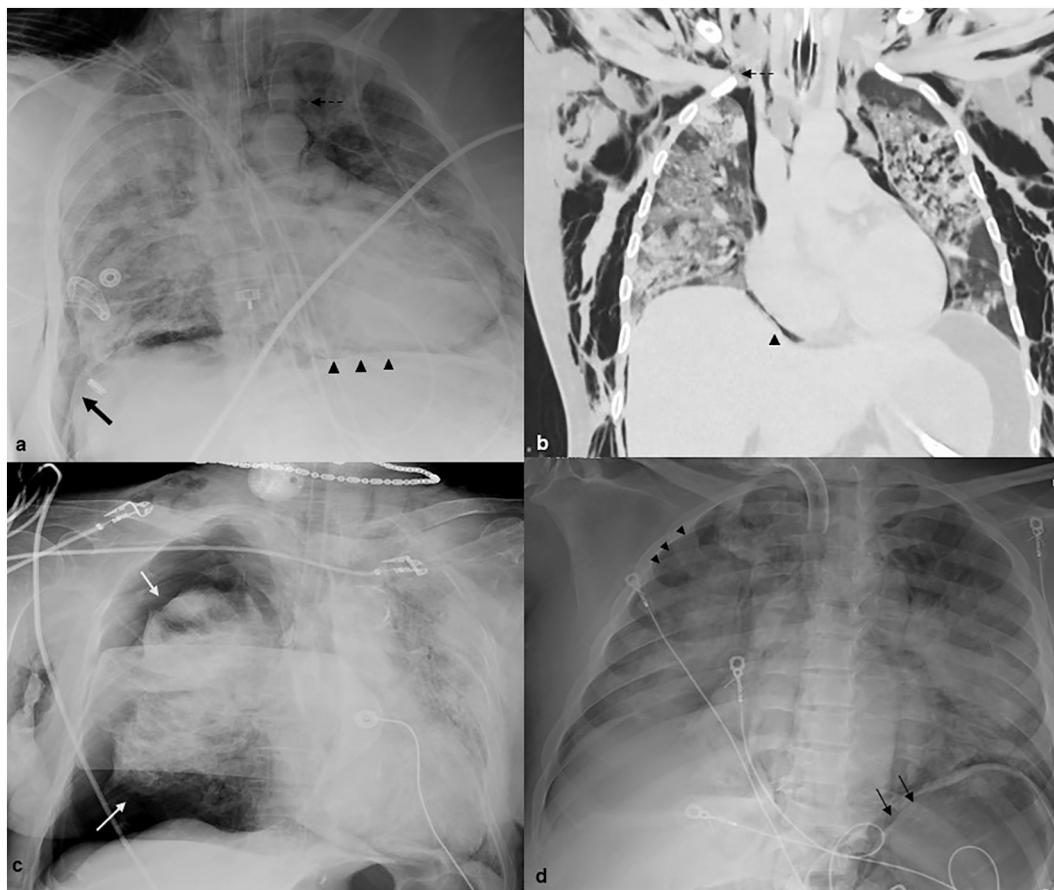

Fig. 2. Chest radiograph findings of barotrauma in multiple intubated patients with COVID-19. a. 63-year-old male with chest radiograph demonstrating pneumomediastinum with the "tubular artery sign" (dashed arrow) and the "continuous diaphragm sign" (arrowheads) seen in pneumomediastinum and the deep sulcus sign (arrow) in the setting of a right pneumothorax. b. Coronal CT from a 40-year-old male demonstrating the appearance of the "tubular artery sign" (dashed arrow) and the "continuous diaphragm sign" (arrowheads) on cross sectional imaging. c. 93-year-old Female with pneumomediastinum and a large right pneumothorax (arrow) with tension morphology resulting in death one day after intubation. d. 46-year-old male with pneumoperitoneum on chest radiograph with a lucent left upper quadrant with air tracking around the stomach contour (arrow) compatible with large volume pneumoperitoneum. A pneumothorax (arrowheads) is also seen.
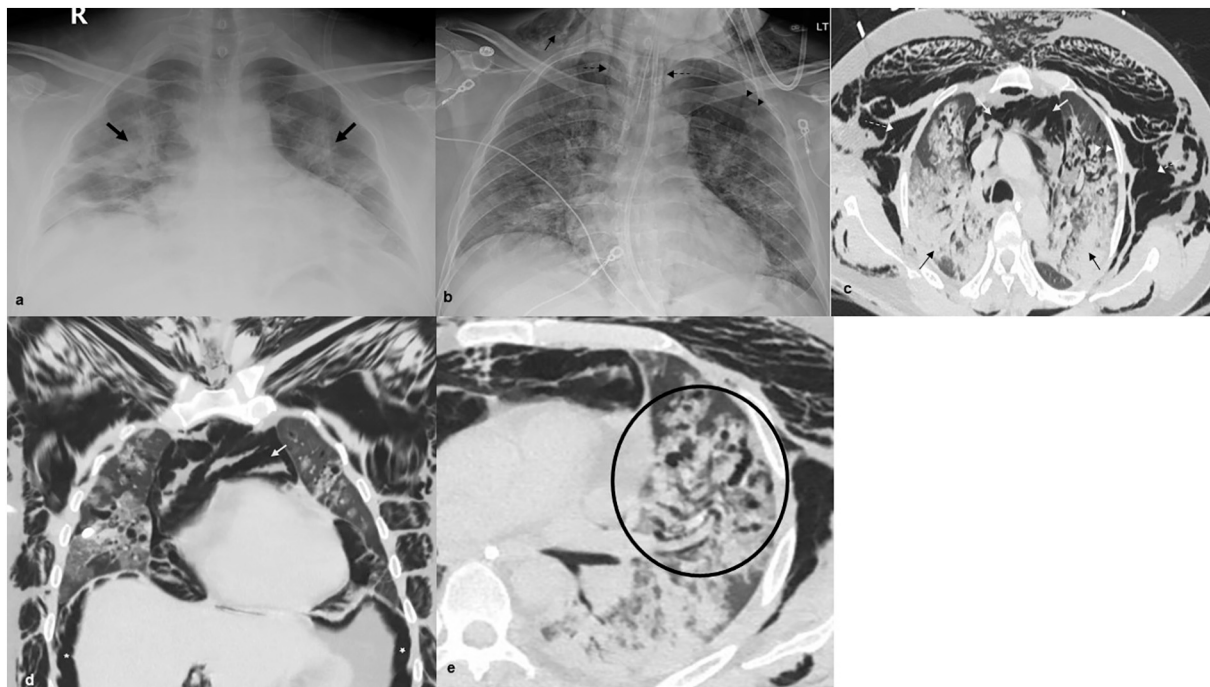
Fig. 3. 40-year-old male with RT-PCR confirmed COVID-19 a. Chest radiograph demonstrating bilateral multifocal opacities (arrows) compatible with COVID-19 pneumonia. b. Pneumomediastinum (dashed arrows), subcutaneous emphysema (arrow), and a left pneumothorax (arrowhead) develop 1 day after intubation. c, d. Axial and coronal chest CT 10 days post intubation demonstrates bilateral ground glass and consolidative opacities (black arrows) with pneumomediastinum (white arrows), air surrounding the pulmonary arterial branches (pulmonary interstitial emphysema) (white arrowheads), extensive subcutaneous emphysema (dashed arrows), and pneumoperitoneum (stars). e. Pulmonary interstitial emphysema (circle).

cases with extensive subcutaneous emphysema, small pneumothoraces and pneumomediastinum may be difficult to appreciate and the chest radiograph should be carefully examined with a high index of suspicion for these associated complications.

4.4. Risk factors

Our results demonstrate that systemic HTN is a statistically significant risk factor for increased mortality in patients with COVID-19. This association is consistent with recently published COVID-19 data[4,35] as well as with the SARS- COV-1 and Middle East Respiratory Syndrome (MERS) literature.[36,37] However, we unexpectedly found both pre-existing HTN and diabetes to be significantly less common in the barotrauma cohort. We originally hypothesized that this may be related to a protective effect from ACE inhibitor or ARB use as data suggests that COVID-19 can enter cells via the angiotensin converting enzyme-2 receptor including surfactant-producing type II pneumocytes.[38,39] This injury could theoretically lead to dysregulation of surfactant production contributing to the development of subcutaneous emphysema and pneumomediastinum from impaired lung compliance and increased surface tension in the alveolar air spaces, analogous to the pathophysiology of PIE development and barotrauma-related air leak in premature neonates. However, there was no significant difference in barotrauma development and ACE or ARB use between patients who developed barotrauma and those who did not. Therefore, the inverse relationship between HTN and the development of barotrauma is still unclear.

4.5. Outcomes

The majority (60%) of patients with barotrauma died prior to the resolution of air with increased odds of death in those with barotrauma in comparison to those without (Table 2). Our findings are consistent with those reported in a similar population from McGuinness et al., which concluded that barotrauma is an independent risk factor for death

in COVID-19. The literature describing the relationship between barotrauma and mortality is complex with many studies reporting an increased risk of mortality in the mechanically ventilated population.[40,41] However, in these studies, barotrauma is likely not the direct cause of death in most patients but rather a marker for illness severity. Of note, there is also a reported association between increased mortality in patients with pneumothoraces in the setting of barotrauma.[6] This may have contributed to the increase in mortality in our barotrauma cohort which demonstrated a significant increased incidence of pneumothorax (40% vs. 3%, $p < 0.001$). Furthermore, in the barotrauma cohort, 8/17 (47%) patients necessitated chest tube placement and one (6%) patient developed a tension pneumothorax resulting in death. These findings underscore the importance of identifying pneumothoraces in these patients in a timely fashion as they can be clinically significant.

In patients who survived, the median time to barotrauma resolution was 5 days. The spontaneous resolution supports the theory that barotrauma is not the direct cause of death in most patients but can lead to complications such as pneumothoraces and is likely a marker for illness severity.[41]

4.6. Limitations

Our findings arose from a multisite healthcare center with evolving protocols over the study period which may have affected outcomes in unpredictable ways. Additionally, the retrospective nature of this study limits what variables can be accurately extracted for analysis.

5. Conclusion

Our results reveal barotrauma as a frequent complication of mechanically ventilated patients with COVID-19 with a mechanism of development related to pulmonary interstitial emphysema. Patients with barotrauma have a higher rate of pneumothoraces and a statistically significant increased risk of death. Clinicians should maintain a

high index of suspicion for these complications when assessing these critically ill patients.

Author contributions

We request that both Sharon Steinberger and Mark Finkelstein are listed as co- first authors as they have made equal contributions to this manuscript.

Andrew Pagano, Sayan Manna, Danielle Toussie, Michael Chung, Adam Bernheim, Jose Concepcion, Sean Gupta, Corey Eber, and Sakshi Dua assisted with study design and critical editing of the manuscript.

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