Alveolar air leak and paraseptal emphysema in severe COVID-19 disease

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Abstract

Background
Corona virus 2019 (COVID-19) pandemic spread in the world as a great medical crisis. Its pathophysiology, manifestations, complications, and management are not completely defined, yet. In this study frequency of alveolar air leak in critically ill COVID-19 subjects is explored.

Methods
A total of 820 critically ill COVID-19 subjects who admitted with respiratory insufficiency to ICUs of Sina University Hospital from March 2020 to June 2021 were included. All their chest x ray (CXR) and Computed tomography (CT) of chest were reviewed. All alveolar air leak episodes (pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema) suspected films reviewed by attending intensivist and radiologist.

Results
Of the 820 ill COVID-19 subjects in ICUs, 492(60%) were male, and 328 (40%) were female. The Mean age of 820 subjects was 60.84 ± 16.82. 584 (71.22%) of subjects were non-intubated, and 236 (28.78%) were intubated. Alveolar air leak occurred in 98 (11.95%) of subjects. Alveolar air leak episodes include pneumothorax in 26 (3.17%), subcutaneous emphysema in 72 (8.78%), pneumomediastinum in 9 (1.10%), and pneumopericardium in 1 (0.12%) of subjects.

The mean age in non-intubated subjects was 59.65 ± 16.84, and for intubated subjects was 63 ± 16.42. There was a significant difference in age between the groups who get intubated, versus not intubated P 0.001.

Of the 584 non-intubated subjects, 31 (5.31%) had subcutaneous emphysema, of the 236 intubated subjects, 41 (17.37%) had subcutaneous emphysema. Difference between groups was statistically significant, $P < 0.001$. When we compared intubated and non-intubated patients in case of total numbers of alveolar air leak episodes, the difference was statistically significant $P < 0.001$.

Conclusion
According to this study, intubation was implemented more in older patients. Also, invasive ventilation was significantly associated with subcutaneous emphysema and total number of alveolar air leak episodes. In every patient with exaggeration of hypoxia, dyspnea or chest pain, pneumothorax should be kept in mind as a differential diagnosis.

Keywords: COVID-19; Respiratory failure; Alveolar air leak; Paraseptal emphysema

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Introduction

Coronavirus is an enveloped, positive single-strand RNA virus. It belongs to the Orthocoronavirinae subfamily, as the name suggests, whose members show characteristic "crown-like" spikes on their surfaces. [1]

In a systematic review [2] to understand the global point estimate of deaths and risk factors for patients is, forty-five studies with 16,561 patients from 17 countries across four continents who were admitted to ICUs with severe COVID-19, were included. Common comorbidities included hypertension (49.5%) and diabetes mellitus (26.6%). More than three-quarters of cases experienced the development of ARDS (76.1%). Invasive mechanical ventilation was required in 67.7% of case, vasopressor support in 65.9% of cases, renal replacement therapy in 16.9% of cases, and extracorporeal membrane oxygenation in 6.4% of cases. The in-hospital mortality rate of 28.1%.

In a prospective, multicenter cohort study (SATICOVID), [3] 1909 invasively ventilated patients with COVID-19 were enrolled. Lung-protective ventilation was widely used. Median tidal volume (V_T) was 6.1 mL/kg predicted body weight on day 1, and the value increased significantly up to day 7, positive end-expiratory pressure was 10 cmH$_2$O (8-12) on day 1, with a slight but significant decrease to day 7. Ratio of partial pressure of arterial oxygen (PaO$_2$) to fractional inspired oxygen (FiO$_2$) was 160 [interquartile range (IQR) 111-218], respiratory system compliance 36 mL/cmH$_2$O (29-44), driving pressure 12 cmH$_2$O (10-14), and FiO$_2$ 0.60 (0·45-0·80) on day 1. Acute respiratory distress syndrome developed in 1672 (87.6%) of patients.

In the same study, ICU mortality was 57 %, 462 (43·8%) patients died of refractory hypoxemia, frequently overlapping with septic shock (174). Age, Charlson score, endotracheal intubation outside of the ICU admission, vasopressor use on day 1, D-dimer concentration, PaO$_2$/FiO$_2$ on day 1, arterial pH on day 1, driving pressure on day 1, acute kidney injury, and month of admission were identified as independent predictors of mortality. The authors concluded that patients with COVID-19 who required invasive mechanical ventilation, lung-protective ventilation was widely used but mortality was high. The sustained burden of COVID-19 on scarce health-care personnel might have contributed to high mortality. These data might help to identify points for improvement in the management of patients in middle-income countries and elsewhere.

It seems, while primary reports of COVID-19, showed disease was more prevalent in older people with comorbidities, gradually younger healthy ones got involved too. The aim of this study is to assess the frequency of alveolar air leak in critically ill COVID-19 patients.

Patients and Methods

In this cross- sectional study, chest imaging of 820 COVID-19 subjects with respiratory insufficiency admitted to ICU of Sina University Hospital from March 2020 to June 2021 were reviewed. Subjects who received non-invasive oxygenation strategies by either nasal cannula, simple mask, reservoir mask, or mask and portable ventilator (NIV) or even on conventional ventilator with non-invasive mode were classified as "non-intubated" group. Subjects on invasive mechanical ventilation via an endotracheal tube or a tracheostomy tube were classified as "intubated" group.

Clinical conditions of air leaks that defines extrusion of air from normal gas-filled cavities including the upper airway, tracheobronchial tree include pneumothorax, pneumomediastinum, pneumopericardium, and subcutaneous emphysema, was assessed.

Barotrauma means injury to body because of changes in barometric (air) or water pressure. Because we do not know whether alveolar rupture is exactly due to pressure trauma of patient respiratory burdens or ventilator pressure or tissue injury due to viral effects, we used alveolar air leak instead of barotrauma.

All alveolar air leak suspected films were reviewed by an attending intensivist and radiologist.

Informed consent was waived, because this study was based on a retrospective analysis of case records from our university hospital. During filing of alveolar air leak imaging, name of patients and center deleted. Permission of radiology data access was provided by the ethics certificate IR.TUMS.SINAHOSPITAL.REC.1400.060.

Statistical analysis

All statistical Analyses were done in Stata software (Version 12). Categorical variables presented as numbers and percentages, and the continuous variable presented as mean $\pm$ standard deviation (SD). Association between consequences of the COVID-19 and receiving ventilation types are tested based on Chi-square-test or Fisher Exact Test. Difference of continuous variables between two groups were tested using independent t-test of Mann-Whitney test. A P-value less than 0.05 is considered statistically significant.

Findings

Patients' characteristics

Of the 820 ill COVID-19 patients in ICUs, 492 (60%) were male, and 328 (40%) were female. The Mean age of subjects was 60.84 $\pm$ 16.82. The minimum age was 14 year, and the maximum was 97 years.

584 (71.22%) of subjects were non-intubated, and 236 (28.78%) were intubated. Fifteen subjects of the intubated

group received bedside percutaneous dilational tracheostomy (PDT).

Alveolar air leak episodes occurred in 98 (11.95%) of COVID-19 subjects requiring ICU admission for respiratory support and monitoring.

Alveolar air leak consisted of pneumothorax in 26 (3.17%), subcutaneous emphysema in 72 (8.78%), pneumomediastinum in 9 (1.10%), and pneumopericardium in 1 (0.12%) of subjects. Eleven patients had more than one form of alveolar air leak.

Association of alveolar air leak and type of ventilation/oxygenation and age

In subjects who received invasive ventilations, the mean age was 63 ± 16.42. In subjects who didn't receive invasive ventilation, the mean age was 59.65 ± 16.84. The intubated group was significantly older than the not intubated group (P 0.001) (Table-1).

Mean age of 328 females was 61.52 ± 16.29, and mean age of 492 males was 60.38 ± 17.16. There was no significant difference between age of men and females in case of ICU admission (P 0.34).

Mean age of the 722 subjects without alveolar air leak was 60.6 ± 16.73, and mean age of 98 subjects with alveolar air leak was 62.6 ± 17.38. There was no statistical significance in case of age and frequency of alveolar air leak episodes (P 0.27).

Similarly, there was no statistically significant difference in case of age and frequency of each alveolar air leak, individually: Pneumothorax (P 0.81), subcutaneous emphysema (P 0.14), and pneumomediastinum (P 0.44) (Table-2).

Likewise, when we used a cut-off of age 40 years, the total number of alveolar air leak between groups above 40 years; 88 of 708 (12.43%) subjects and those below or equal to ≤40 years: 10 of 112 (8.93%) subjects, had at least one form of alveolar air leak. The difference between group with this cut-off and occurrence of alveolar air leak was not statistically significant (P 0.29).

Association of alveolar air leak and type of ventilation/oxygenation and gender

Of the 236 intubated subjects: 98 (41.53%) were females and 138 (58.47%) were males. Of the 584 non-intubated subjects: 230 (39.38%) were females and 354 (60.62%) were males. There was no association between gender and the need for intubation (P 0.57) (Table-3).

Of the 328 females, 33 (10.06%) had alveolar air leak, and of the 492 males, 65 (13.21%) had alveolar air leak. There was no statistically significant difference between gender and occurrence of alveolar air leak (P 0.17). Additionally, there was no statistically significant difference between each alveolar air leak individually (Table 4).

Association of alveolar air leak with type of ventilation/oxygenation (intubate or non-intubate)

Of the 584 non-intubated subjects, 13 (2.23%) had pneumothorax, and of the 236 intubated subjects, 13 (5.51%) had pneumothorax. The difference between frequency of pneumothorax between intubated and non-intubated subjects was not significant (P 0.015).

The difference between non-intubated and intubated subjects in case of pneumomediastinum or pneumopericardium was not statistically significant. Of the 584 non-intubated subjects, 31 (5.31%) had subcutaneous emphysema, and of the 236 intubated subjects, 41 (17.37%) had subcutaneous emphysema. Difference between groups was statistically significant (P <0.001). When we compared intubated and non-intubated subjects in case of total numbers of alveolar air leak episodes, it was statistically significant (P <0.001).

Subcutaneous emphysema and total number of alveolar air leak episodes (sum of subcutaneous emphysema, pneumothorax, pneumomediastinum, and pneumopericardium) was more common in the intubated group (Table-5).

According to our study, intubation and invasive mechanical ventilation were implemented more in older subjects. Also, invasive ventilation was significantly associated with subcutaneous emphysema and total number of alveolar air leak episodes.

Figures 1 - 4, are examples of imaging of alveolar air leak in our subjects

Discussion

Brief review of literature of previous air leak reports

In one study, [4] a high incidence of barotrauma in 601 patients with coronavirus disease 2019 (COVID-19) infection receiving invasive mechanical ventilation (IMV) at New York University Langone Health during the height of the COVID-19 pandemic was observed, with a per-patient rate of 15% and a total rate of 24%. In a historical comparison group of acute respiratory distress syndrome patients on IMV in their institution, 10% of patients experienced barotrauma. According to that study, these high barotrauma rates raise questions of whether coronavirus infections uniquely increase barotrauma risk.

Group	Observed	Mean	SD	P value
Non-intubated	584	59.65	16.84	0.001
Intubated	236	63.78	16.42	
Difference		4.13		

Table-1 Distribution of age (mean ± SD) according to type of ventilation (intubated vs. non-intubated)

Alveolar air leak /No-Alveolar air leak	Age			Total	P value
	Mean	SE	SD		
Pneumothorax	60.07	3.84	19.59	26	0.81
Without Pneumothorax	60.86	0.59	16.73	794	
Difference	0.79	3.35			
Subcutaneous emphysema	63.63	1.85	15.73	72	0.14
Without Subcutaneous emphysema	60.57	0.61	16.90	748	
Difference	3.06	2.07			
Pneumomediastinum	56.55	5.63	16.90	9	0.44
Without Pneumomediastinum	60.89	0.59	16.82	811	
Difference	4.33	5.63			
Pneumopericardium	75			1	
Without Pneumopericardium	60.82	0.58	16.82	819	
Difference	14.17				
All of alveolar air leak cases	62.60	1.75	17.38	98	0.27
Without alveolar air leak	60.60	0.62	16.73	722	
Difference	1.99	1.81			
Total				820	

Table-2 Distribution of age (mean ± SD and SE) according to type of alveolar air leak. SD: standard deviation, SE: standard error

Gender	Ventilation		Total Number (%)	P value
	Intubated Number (%)	Non-intubated Number (%)		
Female	98 (41.53)	230 (39.38)	328 (40)	0.57
Male	138 (58.47)	354 (60.62)	492 (60)	
Total	236	584	820	

Table-3 Distribution of gender according to the type of ventilation (intubated and non-intubated)

Alveolar air leak /No-Alveolar air leak	Gender		Total	P value
	Females Number (%)	Males Number (%)	Number (%)	
Pneumothorax	8 (2.44)	18 (3.66)	26 (3.17)	0.33
Without Pneumothorax	320 (97.56)	474 (96.34)	794 (96.83)	
Total	328	492	820	
Subcutaneous emphysema	25 (7.62)	47 (9.55)	72 (8.78)	0.34
Without subcutaneous emphysema	303 (92.38)	445 (90.45)	748 (91.22)	
Total	328	492	820	
Pneumomediastinum	3 (0.91)	6 (1.22)	9 (1.10)	0.07
Without pneumomediastinum	325 (99.09)	486 (98.78)	811 (98.90)	
Total	328	492	820	
Pneumopericardium	0 (0)	1 (0.20)	1 (0.12)	0.41
Without pneumopericardium	328 (100)	491 (99.80)	819 (99.88)	
Total	328	492	820	
All alveolar air leak cases	33 (10.06)	65 (13.21)	98 (11.95)	0.17
Without alveolar air leak	295 (89.94)	427 (86.79)	722 (88.05)	
Total	328	492		

Table-4 Distribution of gender according to type of alveolar air leak in studied COVID-19 subjects

Alveolar air leak /No-Alveolar air leak	Ventilation/oxygenation state		Total	P value
	Non-intubated Number (%)	Intubated Number (%)	Number (%)	
Pneumothorax	13 (2.23)	13 (5.51)	26 (3.17)	0.01
Without Pneumothorax	571 (97.77)	223 (94.49)	794 (96.83)	
Total	584	236	820	
Subcutaneous emphysema	31 (5.31)	41 (17.37)	72 (8.78)	<0.001
Without subcutaneous emphysema	553 (94.69)	195(82.63)	748 (91.22)	
Total	584	236	820	
Pneumomediastinum	3 (0.51)	6 (2.54)	9 (1.10)	0.01
Without pneumomediastinum	581 (99.49)	230 (97.46)	811 (98.90)	
Total	584	236	820	
Pneumopericardium	0 (0)	1 (0.42)	1 (0.12)	0.29
Without pneumopericardium	584 (100)	235 (99.58)	819 (99.88)	
Total	328	492	820	
All alveolar air leak cases	43 (7.36)	55 (23.31)	98 (11.95)	<0.001
Without alveolar air leak	541 (92.64)	181(76.69)	722 (88.05)	
Total	328	492		

Table-5 Distribution of alveolar air leak in intubated and non-intubated COVID-19 subjects
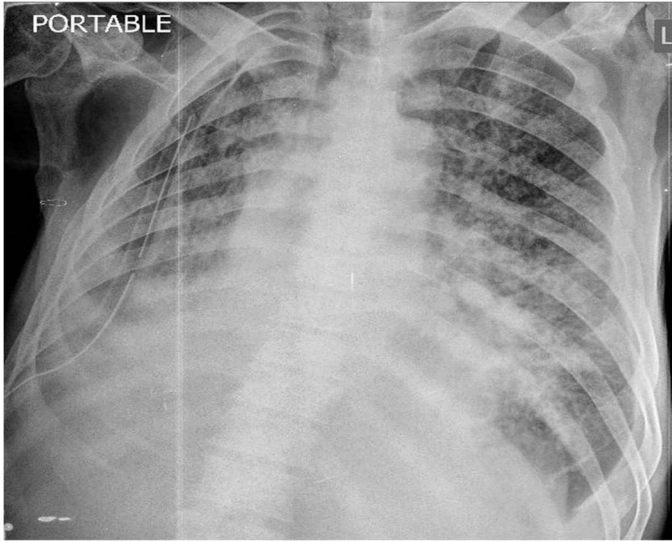
Figure 1: A non-intubated COVID-19 subject with bilateral pneumothorax, subcutaneous emphysema

Figure 3: A COVID-19 subject with pneumomediastinum, possibly evolved to paraseptal emphysema
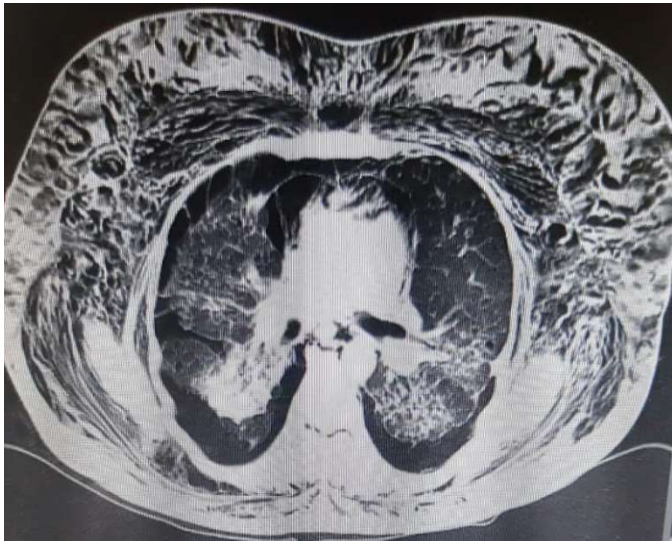

Figure 2: A COVID-19 subject with pneumomediastinum, pneumopericardium, bilateral pneumothorax, and subcutaneous emphysema-possibly paraseptal emphysema
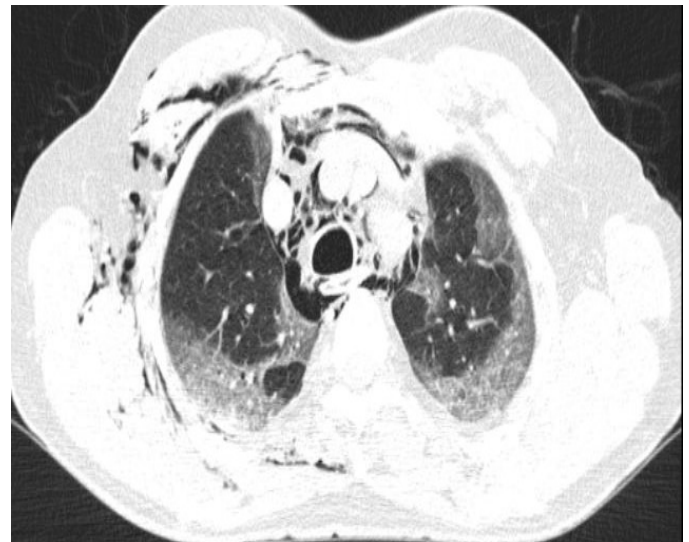

Figure 4: A COVID-19 subject with pneumomediastinum, pneumopericardium, subcutaneous emphysema

In the Middle East Respiratory Syndrome (MERS) epidemic, a pneumothorax rate of 30% was reported in a small study of intensive care unit intubated patients.[5]

In a retrospective analysis [6] of 670 moderate to severe COVID-19 cases, 10 patients developed pneumothorax, pneumomediastinum, pneumopericardium and/ or subcutaneous emphysema - referred to as Alveolar Air leak Syndrome; The incidence of alveolar air leak was found to be 2.39%. According to that study, spontaneous alveolar air leaks are a rare but definite complication of COVID-19 viral pneumonia and may occur in the absence of mechanical ventilation. ICU Clinicians must be alert about the diagnosis and treatment of this complication.

Another study [7] concluded that pneumothorax/pneumomediastinum are rare and life-threatening complication in mechanically ventilated patients with COVID-19. Further research is needed to understand the pathophysiology behind the development of air leak injuries in patients with COVID-19.

A study [8] presented a series of 15 cases that highlight the clinical heterogeneity with respect to stage of illness, ventilatory status, and varied clinical scenarios at the time of development of these syndromes. All cases were diagnosed clinically and confirmed by bedside chest X-ray and were managed promptly. Therefore, high level of clinical suspicion

and vigilance is necessary to identify and manage cases of air-leak syndrome.

Another study [9] presented a case of COVID-19 pneumonia complicated on day 13 post admission by pneumomediastinum, pneumothorax, and subcutaneous emphysema with no identifiable risk factors for such complication. The patient received medical treatment for his COVID-19 infection without the use of an invasive or non-invasive ventilator.

Examples of air leak in other viral pathogens:

A case study [10] reported a patient transferred to the intensive care unit because of declining respiratory status, intubation was performed, and mechanical ventilation was begun on hospital day 4. Shortly thereafter, bilateral pneumothorax and subcutaneous emphysema developed. In summary, the pathologic and imaging findings in this case was consistent with 2009 influenza A (H1N1) infection that progressed to pneumonia, diffuse alveolar damage, and ARDS. Clinical management was further complicated by pulmonary interstitial emphysema and by subsequent development of pneumomediastinum, pneumothorax, and subcutaneous emphysema.

In another study [11] of 13 ICUs in Toronto area of 196 patients with severe acute respiratory syndrome (SARS), 38 (19%) became critically ill. Twenty-nine (76%) of that group, required mechanical ventilation and 10 of these (34%) experienced barotrauma.

Ventilator setting, patient s efforts as other possible etiologies of air leak

In a multicenter randomized trial [12] conducted at 120 intensive care units in 9 countries from November 2011, through April 2017 enrolled adults with moderate to severe ARDS. An experimental strategy with a lung recruitment maneuver and PEEP titration according to the best respiratory system compliance (n = 501; experimental group) or a control strategy of low PEEP (n = 509). All patients received volume-assist control mode until weaning. Compared with the control group, the experimental group strategy had increased 6-month mortality (65.3% vs 59.9%), increased the risk of pneumothorax requiring drainage (3.2% vs 1.2%), and higher risk of barotrauma (5.6% vs 1.6%). These findings do not support the routine use of lung recruitment maneuver and PEEP titration in these patients.

In a study [13] of 22 patients with confirmed SARS-CoV-2 infection on mechanical ventilation, 7 patients developed spontaneous pneumothorax. Chronic obstructive pulmonary disease was not present in any of the patients. Remarkably, the mean peak inspiratory pressure (Ppeak) for these patients was 25 cmH$_2$O and the mean positive end expiratory pressure (PEEP) was 11 cmH$_2$O. Prone positioning was utilized in 57% of patients and 42% of patients received convalescent plasma. The mortality rate was 71% and the 2 patients who survived were discharged to long term acute care hospitals.

The authors concluded: "Traditionally, ventilator associated pneumothorax is associated with a Ppeak greater than 40 cmH$_2$O, which contrasts with the mean Ppeak of 25 cmH$_2$O observed in this study. ARDS secondary to SARS-CoV-2 infection appears to have a completely different pathophysiology than that of traditional ARDS, which is typically managed with low PEEP and Ppeak. Utilizing the ARDS net protocol in patients with ARDS secondary to SARS-CoV-2 may be deleterious. Further investigation is needed to evaluate this hypothesis".

Corona virus disease 2019 (COVID-19) represents the greatest medical crisis encountered in the young history of critical care and respiratory care. [14] During the early months of the pandemic, when little was known about the virus, the acute hypoxemic respiratory failure it caused did not appear to fit conveniently or consistently into our classification of acute respiratory distress syndrome (ARDS). This not only reignited a half-century's long simmering debate over taxonomy, but also fueled similar debates over how PEEP and lung-protective ventilation should be titrated, as well as the appropriate role of non-invasive ventilation in ARDS.

The potential development of patient self-inflicted lung injury (P-SILI) from spontaneous breathing at a supranormal tidal volume generated by high trans-alveolar pressures (> -15 cmH$_2$O) from a combination of high respiratory drive, preserved respiratory muscle strength and near-normal lung volumes should be taken in account. [14,15]

Some investigators observed relatively preserved respiratory system compliance (50-65 mL/cmH$_2$O) with median best PEEP levels of only 8 cmH$_2$O. This led them and others to criticize the use of a pre-defined PEEP such as the ARDS Net PEEP/FIO$_2$ tables and recommended the abandonment in most COVID cases. [14,16,17]

In addition, non invasive ventilation (NIV failure) in non COVID-19 related acute respiratory failure and ARDS was reported with PaO$_2$/FIO$_2$ ratio between 105 to 179 mmHg and is strongly associated with MODS (multiple organ dysfunction syndrome) reflected in elevated illness severity scores and septic shock. [14,18,19,20-25] During COVID-19 a national database study reported NIV failure of 49%. [14,26]

Possible lung tissue changes in COVID-19

Fibrosis: Interstitial lung disease (ILD), Idiopathic pulmonary fibrosis

The co-existence of interstitial lung disease and COVID-19 has been reported, and it has been postulated that patients with COVID-19 have an increased risk for developing interstitial lung disease. [27,28]

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive and fibrosing lung disease of unknown etiology. The rates of pneumothorax reportedly range from 2 to 20% in patients with IPF, which is second highest to the rates occurring in patients with chronic obstructive pulmonary disease (COPD). [29]

Still, more studies are needed to understand the fibrosis pathology and alveolar air leak.

Emphysema

Paraseptal emphysema allude to emphysematous lung changes adjacent to the pleura. [30-33] It is usually seen in combination with other forms of emphysema [34] and is smoking related. Due to its subpleural location, paraseptal emphysema is a risk factor for pneumothorax. [30,34]

A higher burden of paraseptal emphysema was associated with a higher dyspnea score, more exacerbations, reduced lung function, and decreased exercise capacity. Paraseptal emphysema is also a risk factor for pneumothorax. [35,36]

In a case study, [37] a 77-year-old woman with a 40-pack-year smoking history was admitted to the intensive care unit for SARS Cov-2 pneumonia. The admission chest CT scan demonstrated bilateral peripheral ground glass opacities in the right middle lobe with marked paraseptal emphysema in the lower lobes. Four months later, a repeat chest CT showed that the paraseptal emphysematous changes had nearly resolved and had been replaced by a thin linear band of what may represent fibrosis. According to author of that report, the resolution of large emphysematous bullae following infection in that patient, the loss of paraseptal emphysema is perhaps related to the healing phase of the viral pneumonia with loss of the airways communicating with these regions.

Air leak diagnosis

Portable chest X-ray is the first diagnostic evaluation imaging being used and the procedure of choice for the documentation of lung underlying pathology or the presents of intra-vascular lines, tubes, or devices. [38] Nevertheless, they often exhibit diagnostic disadvantages, considering that pneumothoraces in ARDS patients may have unusual, as well as subtle features

and small sized pneumothoraces or loculated pneumothoraces, can be missed on chest X-ray. Furthermore, other types of air leaks, such as pneumomediastinum and interstitial pulmonary emphysema, may be more difficulty observed by chest radiographs. [38]

Chest computed tomography (CT) is more specific, but sometimes it is difficult to transfer an unstable patient for CT scan.

Ultrasound diagnosis of pneumothorax relies on the recognition of four sonographic artifact signs: the lung sliding, the B lines, the lung point, and the lung pulse. [39] Combining these few signs, it is possible to accurately rule in or rule out pneumothorax at the bedside in several different clinical scenarios. Sensitivity of a lung ultrasound in the detection of pneumothorax is higher than that of conventional anterior-posterior chest radiography, and similar to that of computerized tomography.

Subcutaneous emphysema, pleural calcifications or poor acoustic transmission can complicate the diagnosis. [39,40,41,42] In patients with dyspnea, COPD, and pleural adherences lung sliding can be diminished or abolished. [39,43,44] This sign can be the only finding enabling us to distinguish a pneumothorax from a big pleural bulla. [39,45,46] We must remember that lung sliding excludes pneumothorax with a negative predictive value and a sensibility of 100%. [39,40] However, its absence is not a synonym of pneumothorax. In patients in critical condition with massive atelectasis, intubation of the main bronchus, pulmonary contusion, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome or pleural adherences, lung sliding may or may not be seen. [39,43,44] This is why the absence of a sign of lung sliding needs to be combined with other signs if we want to improve the diagnostic efficiency of this test. [39]

Electrical Impedance Tomography (EIT) is a rapidly evolving technology used for bedside lung imaging. EIT has multiple benefits over standard chest imaging techniques; it is non-invasive, it can be used at the bedside, and it allows continuous monitoring of the patient's condition. It is used for monitoring changes in the ventilation and perfusion of lung and early detection of pneumothorax. [47]

In conclusion, we reviewed the imaging of COVID-19 subjects, for those who were imaged with chest CT scan, the emphysematous changes in several of our subjects were noticeable as in image 2. Further studies are needed to explore it and follow the subjects for possible pneumothorax occurrence or vanishing of emphysematous changes of lung.

In this study, we did not correlate air leak to specific lung imaging characteristics, pathology, ventilator setting, dys-

synchrony between patient and ventilator, transpulmonary pressure and intra- esophageal pressure measurements, NIV duration or failure, lung mechanics, compliance, impact of SARS CoV-2 variants, host response, certain treatment modality, type of lung injury, pneumonia, presence of comorbidities, body habitus, level of hypoxia, duration of hypoxia before intubation, demographic or biochemical data or other confounding factors. Total air leak episodes and especially subcutaneous emphysema were noticeable. Pneumothorax should be suspected as a differential diagnosis in any patient with deterioration of hypoxia and dyspnea. Frequent lung exam, respiratory rate, and efforts, and serial CXR in need are necessary for early recognition of alveolar air leak. Respiratory follow-up of patients with severe disease is recommended.

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