Original article

J Nepal Health Res Counc 2021 Jul-Sep;19(52): 460-6

DOI: https://doi.org/10.33314/jnhrc.v19i3.3612

Pneumomediastinum in COVID-19 Patients with Acute Respiratory Distress Syndrome

Bidushi Pokhrel,[1] Gauri Adhikari,[1] Raju Pangeni,[2] Pradeep Raj Regmi,[3] Anish Baniya[4]

ABSTRACT

Background: Pneumomediastinum, an uncommon entity, has been on the rise with increasing cases of COVID-Acute respiratory distress syndrome. It has been unclear whether this entity represents an indicator of poor clinical outcome or not. The aims of this study were to find out the incidence of pneumomediastinum in COVID-Acute respiratory distress syndrome patients, describe their clinical characteristics and try to explain its plausible mechanisms..

Methods: A descriptive, cross-sectional study was carried out in the ICU of our hospital among 280 patients admitted with COVID-Acute respiratory distress syndrome over a period of 6 months. Demographics along with various clinical, laboratory, and radiological parameters were analyzed. Relevant statistical analyses were done to summarize our findings.

Results: The incidence of pneumomediastinum in COVID-ARDS patients was 2.8%. All patients were male, none had pulmonary co-morbidities and six of them (60%) were on invasive mechanical ventilation. All intubated patients were on lung protective mechanical ventilation. The median PEEP, peak airway pressure and plateau pressure were 10 (IQR: 4), 29 (IQR: 8) and 28 (IQR: 4) respectively. The mean CT severity score was 22.7 (SD: 1.64). Five patients died after 6.8 days (SD: 4.8) of diagnosis. The average hospital stay was of 34 days.

Conclusions: Pneumomediastinum is a possible complication of COVID-Acute respiratory distress syndrome which could signify the disease severity and vice versa. Furthermore, it could be an indicator of relatively poor prognosis and therefore requires larger studies to establish the association.

Keywords: ARDS; COVID-19; macklin effect; Nepal; pneumomediastinum

INTRODUCTION

COVID-19 has proven to be a Pandora's Box, with studies reporting newer clinical manifestations, diagnostic advancements and modalities of treatment every day. Among some of the unusual complications of this disease, pneumomediastinum in COVID-19 ARDS has been sparsely reported in literature.[1] Pneumomediastinum (PM) is the presence of air in the mediastinum, and is usually abnormal, being attributed to trauma (iatrogenic or non-iatrogenic), thoracic surgeries, esophageal rupture, intrinsic lung and airway diseases to name a few.[2] On its own, this condition is not typically life-threatening, often resolving with conservative treatment. However, it may indicate the presence of severe underlying pathology.[3]

In COVID-19, incidence of PM has been increasing in comparison to its rarity before the emergence of this pandemic. We present the cases of COVID-ARDS patients with spontaneous PM managed in the Intensive Care Unit (ICU) of our hospital and attempt to explore their characteristics herein.

METHODS

We analyzed data from patients who were admitted in our COVID-ICU from August 2020 to January 2021 who subsequently developed PM. A positive RT-PCR for Severe Respiratory Corona Virus Disease-2 (SARS Cov-2), a documented clinical or radiological diagnosis of COVID-ARDS confirmed by a high-resolution computed tomography (HRCT) or chest X-ray (CXR) were the predetermined inclusion criteria. Classification and diagnosis of COVID-19 pneumonia with ARDS was done as per World Health Organization (WHO) criteria.[4]

Relevant data were extracted from Electronic Medical Record (EMR) system of the hospital and organized in a pro forma. Diagnosis and quantification of PM was made with the help of radiological investigations performed and reviewed by board certified radiologist. Findings

Correspondence: Dr Bidushi Pokhrel, Intensive Care Unit, Hospital for Advanced Medicine and Surgery, Dhumbarahi, Kathmandu, Nepal. Email: pbidushi@gmail.com, Phone: +9779849580766.

of the study were summarized by calculating mean, median and standard deviation and presented in the form of numbers and percentages.

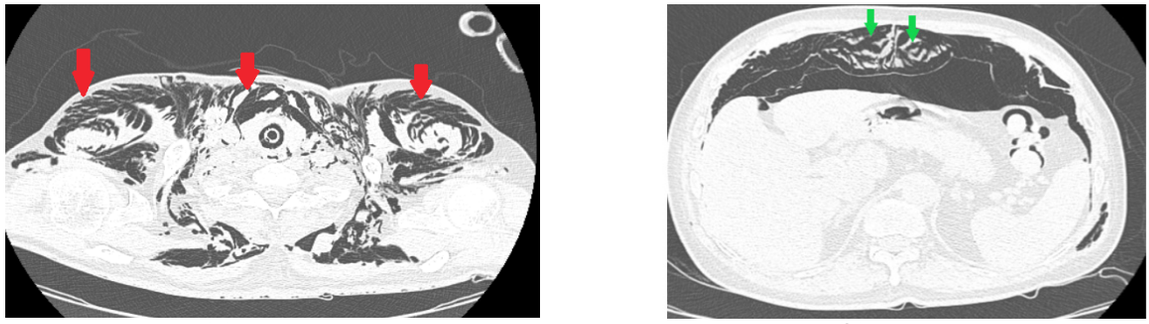
Informed consent was taken from either the patients or their family members and Ethical approval was obtained from Nepal Health Research Council (Ref no 2524).

RESULTS

Out of 280 patients admitted to our ICU with the diagnosis of COVID-19 ARDS, ten (2.8%) were detected to have PM, All patients were males with median age of 62 years [Interquartile range (IQR): 16] and none of them had pulmonary comorbidities. Majority (90%) were non-smokers. As part of hospital protocol, all of them had received supplemental oxygen, antivirals, corticosteroids and anticoagulants along with other supportive measures. The presence of PM was detected after median 11 days of hospitalization (IQR: 14). Rapid worsening of oxygen saturation raised the clinical suspicion of PM, only four patients had subcutaneous emphysema. Six patients were on non-invasive ventilation (NIV), including four on high flow nasal cannula (HFNC) prior to the detection of PM. Three of these subsequently needed invasive ventilation.

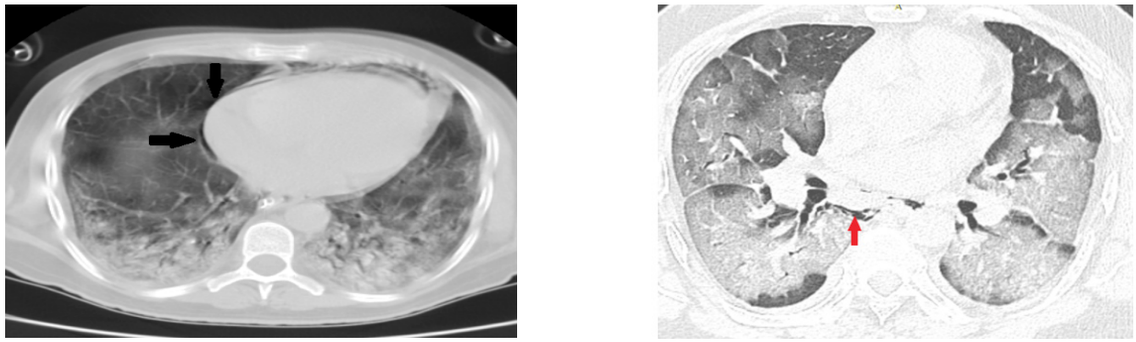
The median positive end expiratory pressure (PEEP) among the patients receiving NIV and invasive ventilation was 10 (IQR: 4), median observed peak airway pressure (PAW) and plateau pressure (Pplat) before the development of PM were 29 (IQR: 8) and 28 (IQR: 4) respectively. The patients who received oxygen support via HFNC were provided flow rates of maximum 60 L/min. Three of the intubated patients developed PM before intubation while three developed it at least 24 hours after intubation; however none showed other signs of possible iatrogenic trauma while intubating. One patient had received supplemental oxygen through non rebreather mask (NRM) with a peak flow up to 15L/min. The average number of days from symptom onset to the development of PM was 16. 5 days (SD: 8.74)

HRCT images of all the patients showed typical changes of COVID-19 pneumonia (bilateral ground glass opacities/ consolidation/ crazy paving/ reticulo-nodular opacities/ fibrosis) with minimal to diffuse PM (Figures 1-3). The mean CT severity score was found to be 22.7 (SD: 1.64). Two (20%) of them had co-existing pneumothorax requiring tube thoracostomy.



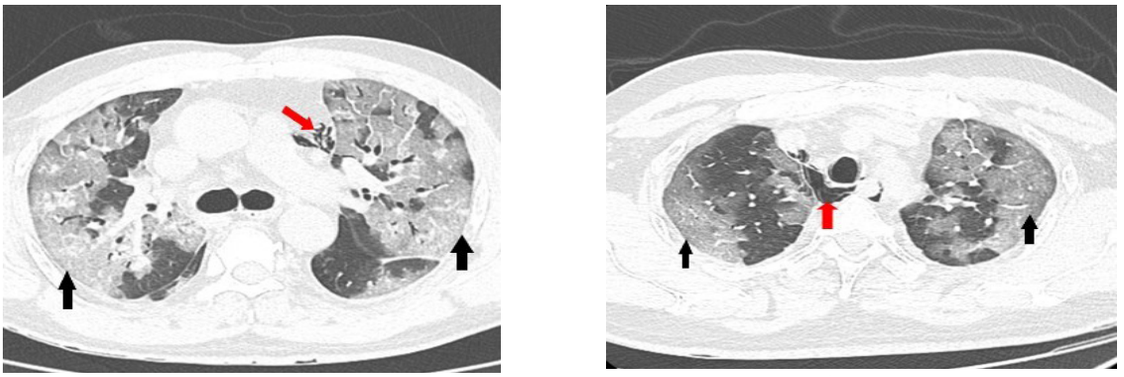
(a) (b)

Figure 1. (a) Axial HRCT images show extensive free air in subcutaneous, fascial and intramuscular compartments and outlining the great vessels of neck (red arrows). Endotracheal tube in-situ. (b) Pneumoperitoneum and free air within the muscles of anterior abdominal wall (green arrows).



(a) (b)

Figure 2. (a) and (b). Axial HRCT images show pneumopericardium (black arrows) and air along the peribronchial sheath of superior segmental bronchi of right lower lobe (red arrow). Predominant peripheral consolidation and ground glass opacities related to COVID-19 are seen.



(a) (b)

Figure 3. (a) and (b). Pneumomediastinum (red arrows). Extensive peripheral ground glass opacities and crazy paving in bilateral lung fields (black arrows).

Table 1. Initial demographic, clinical and laboratory parameters of COVID-19 patients developing pneumomediastinum.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age/ Sex	53/M	58/M	55/M	74/M	37/M	66/M	70/M	40/M	69/M	68/M
Presenting complaints										
Fever	-	6 days	7 days	5 days	16 days	11 days	-	5 days	-	2 days
Cough	5 days	-	4 days	-	-	10 days	7 days	5 days	7 days	2 days
SOB	2 days	4 days	2 days	2 days	2 days	9 days	7 days	5 days	7 days	1 day
Pulmonary comorbidities	None	None	None	None	None	None	None	None	None	None
Non-pulmonary comorbidities	HTN Hyperuricemia Dyslipidemia	DM	DM HTN	None	None	DM HTN BEP Hypothyroidism	DM Dyslipidemia	DM Depressive Disorder	DM Depressive disorder	DM HTN
Smoking status	Non-smoker	Non-smoker	Smoker	Non-smoker	Non-smoker	Non-smoker	Non-smoker	Non-smoker	Non-smoker	Non-smoker
Maximum RR	42	40	50	45	42	34	48	45	50	32
O2 requirement on admission	NIV; FiO_2-70%, PEEP-8, PS-8	IMV; AC/VC, FiO_2-60%, PEEP-14, PS-8	VM; FiO_2-30%	NIV; FiO_2-35%, PEEP-8, PS-8	VM; FiO_2-60%	NIV; FiO_2-40%, PEEP-5, PS 10	NP at 3L/min	15L/min via NRM	NP at 2L/min	NP at 4L/min
Maximum oxygen support	NIV; FiO_2-70%, PEEP- 8, PS-8	IMV; AC/VC, FiO_2-60%, PEEP-14	IMV; AC/VC, FiO_2-90%, PEEP-10	HFNC; FiO_2-90% , Flow-40L/min	IMV; AC/VC, FiO_2-100%, PEEP-12	HFNC, FiO_2-40%, Flow-30L/min	IMV; AC/VC, FiO_2-80%, PEEP-12	IMV; AC/VC, FiO_2-80%, PEEP-10	HFNC; FiO_2-80%, Flow-50L/min	IMV; AC/VC, FiO_2-100%, PEEP-12
Days from symptom onset to event	5	6	17	14	30	23	23	5	21	21
Days from admission to event	0	0	10	9	14	12	16	0	14	19
Total count/ mm^3 (4000-11000)	8110	15590	5510	4210	24680	13130	5570	8380	12100	5800
Lymphocytes % (20-45)	10	95	86	70	94	91	15	08	6	05

Neutrophils % (40-75)	83	01	09	26	04	06	80	84	91	80
CRP mg/dl (<6)	48	96	48	48	96	6	12	22	48	24
D-Dimer ng/ml (<500)	670	5570	1369	760	250	5595	283	809.1	407.34	337
LDH U/L (225-450)	1726	644	641	780	867	579	715	1428	982	521
Ferritin ng/ml (21.8-274.6)	722.7	850.8	243.98	19.9	1247	808	323.96	491.7	953.39	244

Legend: M:Male, SOB: shortness of breath, HTN: hypertension, DM: diabetes mellitus, BEP: benign enlargement of prostate, RR: respiratory rate, FiO_2: fraction of inspired oxygen, NIV: non-invasive ventilation, PEEP: positive end-expiratory pressure, PS: pressure support, IMV: invasive mechanical ventilation, AC/VC: assist control/volume control, NP: nasal prong, NRM: non-rebreather mask, VM: venturi mask, HFNC: high flow nasal cannula, LDH: lactate dehydrogenase, CRP: c-reactive protein

Table 2. Ventilator parameters, imaging characteristics and in-hospital outcomes of COVID-19 patients developing pneumomediastinum.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
FiO_2 before the event	70%; NIV	60%; IMV, AC/VC	70%; HFNC, Flow-50L/min	60%; HFNC, Flow-60L/min	50%; IMV, AC/VC	50%; HFNC, Flow-50L/min	60%; HFNC, Flow-60L/min	80%; NRM, Flow-15L/min	60%; VM	60%; IMV, AC/VC
FiO_2 after the event	70%; NIV	60%; IMV, AC/VC	60%; IMV, AC/VC	90%; HFNC, Flow-40L/min	100%; IMV, AC/VC	50%; HFNC, Flow-30L/min	30%; IMV, AC/VC	80%; IMV, AC/VC	60%; VM	100%; IMV, AC/VC
Intubation	No	2 days before detection of PM	7 hours after detection of PM	No	2 days before detection of PM	No	1 day before detection of PM	2 hours after detection of PM	No	7 days after detection of PM
Peak airway pressure before the event	N/A	35	21	N/A	28	N/A	34	30	N/A	26
Plateau pressure before the event	N/A	30	24	N/A	29	N/A	29	25	N/A	27
Imaging finding (CT/CXR)	Minimal PM F/S/O COVID-19 pneumonia	Moderate PM with pleural/pericardial effusion F/S/O COVID-19 pneumonia	Large PM, pneumoperitoneum and SE F/S/O COVID-19 pneumonia	Diffuse PM with SE F/S/O COVID-19 pneumonia	Left sided pneumothorax with diffuse PM and SE F/S/O COVID-19 pneumonia	Diffuse PM with SE F/S/O COVID-19 pneumonia	Moderate PM with SE F/S/O COVID-19 pneumonia	Moderate PM with SE F/S/O COVID-19 pneumonia	Diffuse PM with SE F/S/O COVID-19 pneumonia Repeat CT: Minimal B/L pneumothorax and increased SE	Moderate PM with SE F/S/O COVID-19 pneumonia
CT severity score (out of 25)	24	22	23	21	24	24	24	23	21	23
In-hospital outcome	Discharged after 8 days without requirement of O_2	Discharged after 45 days on 1L/min O_2 via NP	Expired on 23rd day of admission, or 13th day of detection of PM	Expired on 14th day of admission, or 6th day of detection of PM	Discharged after 69 days of stay on O_2 supplementation via VM	Discharged after 20 days of stay on 1L/min O_2 via NP	Expired on 26th day of admission, or 10th day of detection of PM	Discharged after 28 days of stay without requirement of O_2	Expired on 19th day of admission, or 4th day of detection of PM	Expired on 19th day of admission, or on the day of detection of PM

Legend: FiO_2: fraction of inspired oxygen, NIV: non-invasive ventilation, IMV: invasive mechanical ventilation, AC/VC: assist control/volume control, NP: nasal prong, NRM: non-rebreather mask, VM: venturi mask, HFNC: high flow nasal cannula, PM: pneumomediastinum, SE: subcutaneous emphysema, CT: computed tomography, CXR: chest x-ray, F/S/O: features suggestive of, B/L: bilateral, N/A: not applicable

After the mean hospital stay of 34 days (SD: 23.7), five (50%) of them were discharged home with marked clinical improvement while five (50%) of them died during ICU stay after 6.8 days (SD: 4.8) of the detection of PM. As compared to overall COVID- ICU mortality rate of 17% (Figure 4), this number indicates poor outcome in those who develop PM during hospitalization. The clinical, laboratory and demographic characteristics of the patients on initial presentation, imaging and ventilator parameters are summarized in Tables 1 and 2.

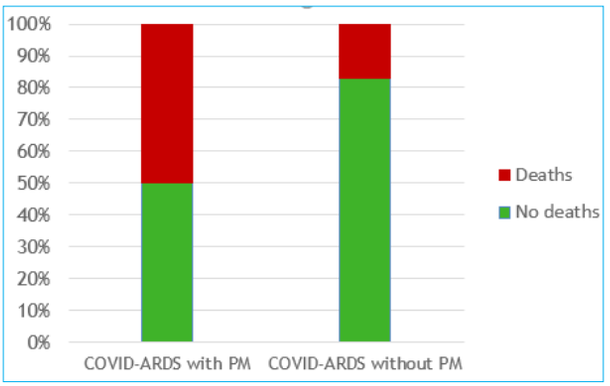


Figure 4. Representation of COVID-ARDS deaths in patients with pneumomediastinum(PM) versus those without pneumomediastinum.

DISCUSSION

Because COVID-19 is 'novel' in its nature such that it has been exhibiting multitude of clinical presentations and the course of the disease progression, its long-term implications and management strategies are being explored every day, it is rather challenging to explain how these vignettes are occurring. Numerous studies have tried to explain the mechanism of development of PM and co-existing SE in relation to a phenomenon known as the Macklin effect, whereby alveolar rupture occurs in the setting of diffuse alveolar damage (DAD),[5] leading to pulmonary interstitial emphysema (air dissection along the bronchovascular sheaths).[6] This air further dissects into the subcutaneous planes and manifests as cervicothoracic SE. The reason for this alveolar rupture could be attributed to the increase in pressure gradient between the alveoli and the interstitial space with the use of positive end-expiratory pressure (PEEP) delivering devices like MV, NIV or even HFNC with high flow.[7, 8] The presence of PM despite lung protective ventilation strategy and relative rarity of this entity in those with non-COVID ARDS managed with NIV suggest 'Macklin effect' to be the most plausible mechanism in numerous studies.[5-7]

This finding is consistent with few other studies [9-11] which have found no definite correlation between barotrauma and MV settings. Furthermore, high pressures generated in activities like coughing, which are not adequately recorded could also contribute to 'barotrauma' in the background of lung damage and decreased lung compliance. [12] PM independent of intubation or positive pressure ventilation has been previously reported in patients with Severe Acute Respiratory Syndrome (SARS), pneumocystis pneumonia, Staphylococcal pneumonia, cytomegalovirus and influenza bronchiolitis,[13-15] all of which were not the etiologies in our case.

The development of PM has been linked to various risk factors such as male gender, smoking, use of recreational drugs and pulmonary comorbidities to name a few.[16,17] In the ICU setting, the incidence of pulmonary air leak disorders in patients on mechanical ventilation ranges from 15 to 40% , almost always associated with underlying parenchymal disease or airflow obstruction.[18] All of our patients were males, which is consistent with the findings of other studies. However, other aforementioned risk factors were not evident in our study.[16,17] Additionally, all our patients had high CT severity scores (>20/25), which is directly correlated with clinical severity of COVID-19,[19] thus increasing the chances of development of PM. Similar to other studies which have attributed PM to poorer prognosis in COVID-19, [1,20] we had similar observations with mortality in 50% patients with PM in comparison to only 17% mortality in the patients without PM. However, further studies with larger sample sizes are required to establish any correlation between the development of PM and grave outcomes for patients.

This study found out the incidence of PM in COVID-ARDS patients of 2.8%, which is lower than that seen in other studies (5.8% in a study of Loffi et. al.,[21] 13% in study of Lemmers et. al.[9]) and even lower than the incidence (11.6%) seen in SARS pandemic of 2004 AD.[13] This inconsistency could have been the result of not carrying out CT imaging invariably in all COVID-19 patients, usually asymptomatic nature of the condition, under-detection or single site and limited cases in our study.

Our study was done in only one hospital and the study population was also small, so our findings cannot be generalized. Because of its retrospective design involving extraction of recorded information, observer bias could have occurred. Recall bias is likely to be present owing to self-reporting of the symptoms and their duration by the patients. Clinical outcomes of the patients who were discharged on request could not be followed up. Since all the patients did not undergo routine chest CT during admission or on their first contact with their physician, exact time of occurrence of PM cannot be definitively

mentioned.

CONCLUSIONS

Pneumomediastinum is a possible complication of COVID-19 ARDS with high morbidity and mortality. Multiple mechanisms can be involved in the pathogenesis of this condition. It could be correlated to the disease severity; however outcomes cannot be generalized. Further studies are required to propose definite implications of PM in relation to COVID-19.

Author Affiliations

[1]Intensive Care Unit, Hospital for Advanced Medicine and Surgery, Dhumbarahi, Kathmandu, Nepal

[2]Department of Pulmonary and Critical Care Medicine, Hospital for Advanced Medicine and Surgery, Dhumbarahi, Kathmandu, Nepal

[3]Department of Radiology, Hospital for Advanced Medicine and Surgery, Dhumbarahi, Kathmandu, Nepal

[4]Department of Emergency Medicine, Hospital for Advanced Medicine and Surgery, Dhumbarahi, Kathmandu, Nepal

Competing interests: None declared

REFERENCES

1. Al-Azzawi M, Douedi S, Alshami A, Al-Saoudi G, Mikhail J. Spontaneous Subcutaneous Emphysema and Pneumomediastinum in COVID-19 Patients: An Indicator of Poor Prognosis? Am J Case Rep. 2020;21:e925557. [PubMed]
2. Kouritas VK, Papagiannopoulos K, Lazaridis G, Baka S, Mpoukovinas I, Karavasilis V, et al. Pneumomediastinum. J Thorac Dis. 2015;7(Suppl 1): S44-9. [PubMed]
3. Manna S, Wruble J, Maron SZ, Toussie D, Voutsinas N, Finkelstein M, et al. COVID-19: A Multimodality Review of Radiologic Techniques, Clinical Utility, and Imaging Features. Radiol Cardiothorac Imaging. 2020; 2(3):e200210 [Article]
4. World Health Organization. Clinical management of COVID-19: Interim guidance. 2020. https://www.who.int/publications/i/item/clinical-management-of-covid-19
5. Konopka KE, Nguyen T, Jentzen JM, Rayes O, Schmidt CJ, Wilson AM, et al. Diffuse alveolar damage (DAD) resulting from coronavirus disease 2019 Infection is Morphologically Indistinguishable from Other Causes of DAD. Histopathology. 2020; 2020;77(4):570–8. [PubMed]
6. Murayama S. Spontaneous pneumomediastinum and Macklin effect: Overview and appearance on computed tomography. World J Radiol. 2014;6(11):850-4. [PubMed]
7. Manna S, Maron SZ, Cedillo MA, Voutsinas N, Toussie D, Finkelstein M, et al. Spontaneous subcutaneous emphysema and pneumomediastinum in non-intubated patients with COVID-19. Clin Imaging. 2020;67:207–13. [PubMed]
8. Raoof S, Nava S, Carpati C, Hill NS. High-Flow, Noninvasive Ventilation and Awake (Nonintubation) Proning in Patients With Coronavirus Disease 2019 With Respiratory Failure. Chest. 2020;158(5):1992–2002. [PubMed]
9. Lemmers DHL, Abu Hilal M, Bnà C, Prezioso C, Cavallo E, Nencini N, et al. Pneumomediastinum and subcutaneous emphysema in COVID-19: barotrauma or lung frailty? ERJ Open Res. 2020;6(4):00385-2020. [PubMed]
10. Anzueto A, Frutos–Vivar F, Esteban A, Alía I, Brochard L, Stewart T, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. Intensive Care Med. 2004;30(4):612–9. [PubMed]
11. Weg JG, Anzueto A, Balk RA, Wiedemann HP, Pattishall EN, Schork MA, et al. The Relation of Pneumothorax and Other Air Leaks to Mortality in the Acute Respiratory Distress Syndrome. Surv Anesthesiol. 1998;338(5):341-6. [PubMed]
12. Udi J, Lang CN, Zotzmann V, Krueger K, Fluegler A, Bamberg F, et al. Incidence of Barotrauma in Patients With COVID-19 Pneumonia During Prolonged Invasive Mechanical Ventilation – A Case-Control Study. J Intensive Care Med. 2020;36(4):477–83. [PubMed]
13. Chu CM, Leung YY, Hui JYH, Hung IFN, Chan VL, Leung WS, et al. Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome. Eur Respir J. 2004;23(6):802–4. [PubMed]
14. Olliff JFC, Williams MP. Radiological appearances of cytomegalovirus infections. Clin Radiol. 1989;40(5):463–7. [PubMed]
15. Silva C, Almeida AF, Ferraz C, Nunes T, Guedes Vaz L. Spontaneous Pneumothorax With Subcutaneous Emphysema: A Rare Complication of Respiratory Syncytial Virus Infection. J Clin Med Res. 2016;8(3):260–2. [PubMed]
16. Banki F, Estrera AL, Harrison RG, Miller III CC, Leake SS, Mitchell KG, et al. Pneumomediastinum: etiology and a guide to diagnosis and treatment. The American Journal of Surgery. 2013 Dec 1;206(6):1001-6. [Article]
17. Cheng Y, Huang T, Lin C, Lee S, Tzao C, Chen J-C, et al. The impact of smoking in primary spontaneous pneumothorax. J Thorac Cardiovasc Surg. 2009;138(1):192–5. [PubMed]

18. Romfh RF. Subcutaneous and mediastinal emphysema. J Am Coll Emerg Physicians. 1972;1(2):35–7. [Article]

19. Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30(12):6808–17. [PubMed]

20. Kangas-Dick A, Gazivoda V, Ibrahim M, Sun A, Shaw JP, Brichkov I, et al. Clinical Characteristics and Outcome of Pneumomediastinum in Patients with COVID-19 Pneumonia. J Laparoendosc Adv Surg Tech. 2020;31(3):273-8 [Article]

21. Loffi M, Regazzoni V, Sergio P, Martinelli E, Stifani I, Quinzani F, et al. Spontaneous pneumomediastinum in COVID-19 pneumonia. Monaldi Arch Chest Dis. 2020;90(4):604–7. [PubMed]