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INTEGRATED STUDY MASTER'S THESIS

Pneumothorax in COVID-19 Patients

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1. Table of Contents:

2. Abbreviations: (in alphabetical order)

ACE-2: Angiotensin-Converting-Enzyme 2

ARDS: Acute Respiratory Distress Syndrome (Syn.: SRF: Severe Respiratory Failure)

CPAP: Continuous Positive Airway Pressure

COPD: Chronic Obstructive Pulmonary Disease

CRS: Cytokine Release Syndrome

CS: Cytokine Storm

DAD: Diffuse Alveolar Damage

ED: Emergency Department

ICU: Intensive Care Unit

ILD: Interstitial Lung Disease

MERS: Middle East Respiratory Syndrome

PEEP: Positive End-Exspiratory Pressure

PMS Pneumomediastinum

PTX: Pneumthorax (PSP: Primary, SSP: Secondary Spontaneous Pneumothorax)

RA: Rheumatoid Arthritis

SARS: Severe Acute Respiratory Syndrome

SARS-COV-1: Endemic in China 2002/3.

SARS-COV-2: Syn. SARS-COVID-19

VATS: Video-Assisted Thoracic Surgery

3. Abstract / Summary:

Introduction:
Spontaneous Pneumothorax (SP) and Spontaneous Pneumomediastinum (SPM) are potential complications of underlying lung diseases, especially forming cystic disorders of the lung with blebs or bullae.
Spontaneous pulmonary barotrauma as Pneumothorax, Pneumomediastinum and subcutaneous emphysema is a rare, but severe complication in COVID-19.

Methods:
The literature research was performed using Key words: Barotrauma / Pneumothorax in COVID-19 patients, Pathophysiology, Radiologic Findings, Histopathology, Treatment. Research for metaanalysis, systematic reviews, prospective studies, case studies, etc.

Results:
In COVID-19 patients, a dysregulated and hyper-activated immune response rather than the virus itself may cause a „Cytokine Storm“ (CS), leading to severe pneumonia and ARDS, thus heavily damaging the lung tissue and alveolar wall.
Increased pressure from pronounced coughing and / or mechanical ventilation even in patients without preexisting lung diseases as COPD may lead to rupture of the alveolar wall and the development of pneumothorax / pneumomediastinum.
In histologic sections of deceased COVID-19 patients, areas of destroyed alveolae were seen with build-up of cystic lesions. Furthermore, there were areas of no significant inflammation in neighbourhood of severely damaged lung tissue, possibly leading to unequal airway pressure and flow with overexpansion and subsequent shear forces in the small airways.
In case of immunocompromised patients or as a result of Corticosteroid medication, bacterial or fungal secondary superinfection can cause lung abscess, pleural empyema and bronchopleural fistula, as shown in some case studies.

Conclusions:
All these mechanisms in COVID-19 pneumonia can lead to pneumothorax and / or pneumomediastinum, increasing the risk of in-hospital mortality by almost four times, especially among the elderly.
Thus – if mechanical ventilation is required - strategies of „Protective Mechanical Ventilation“ with limitations of pressure and volume are important.
In COVID-19-induced ARDS it is recommended to place chest tubes even in small pneumothoraces as lung capacity may be highly reduced.
In case of persistent pneumothorax or if a bronchopleural fistula is suspected, minimal-invasive thoracic surgery / Video-Assisted Thoracic Surgery (VATS) may be required.

4. Introduction:

Though there are 7 Coronaviruses known to be pathogenous to humans (1), until now only SARSCOVID-19 has caused a severe pandemic.

In 2002/3 SARS-COVID-1 appeared in Southern China and resulted in 774 deaths out of 8100 infected individuals in 29 countries.

MERS (Middle East Respiratory Syndrome) originated in Saudi Arabia and was responsible for 848 deaths among 2458 individuals in 27 countries through July 2012.

After SARS-COVID-19 / SARS-COVID-2 was first reported from Wuhan, China in December 2019, it spread rapidly worldwide and was declared a pandemic by the World Health Organization (WHO) on March 12, 2020.

Since then, the virus has had a devastating effect on human life, health systems and economies. Until now it is responsible for about 7 million deaths out of 775 million infected persons (WHO Data COVID-19 dashboard,7/2024).

The pandemic spread was supported by a high contagiosity and infectivity and the capability of the virus to quickly change its surface antigens.
One of the most significant variants of COVID-19-virus up to now was the Delta variant, causing more severe disease to result in hospitalization in the unvaccinated. First designated by the WHO as a variant of concern (VOC) in May 2021 (2), the Delta variant had already outpaced the other variants all over the world by late spring 2021 and showed to be more transmissible and aggressive than the previous strains.

A significant proportion of COVID-19 infections remain asymptomatic or show only mild symptoms, about 20% of cases are severe and over-all mortality is approximately 1%.
The most common presenting clinical symptoms in COVID-19 infection are a sore throat, weakness, fever and cough in addition to other non-specific symptoms including dyspnea, headache, muscle soreness and fatigue.
However, the disease can rapidly progress to severe pneumonia, multiple organ involvement including renal failure, vascular thrombosis, ischemia, respiratory distress and gastrointestinal symptoms,
In addition to the lungs, SARS-COV-2 virus was detected in several other organs, including the heart, liver, kidneys, gastrointestinal tract, spleen, lymph nodes, skin and placenta (3).

There are three consecutive stages of increasing severity (3):

1. The early stage is characterized by flu-like symptoms, mainly due to viral infection itself. Subsequently, patients can develop viral pneumonia, requiring hospitalization or even mechanical ventilation.

2. The second stage is characterized by pulmonary inflammation and coagulopathy, which can develop consecutively but often overlap. Increased levels of inflammatory biomarkers such as Creactive protein (CRP), ferritin, interleukines (1 and 6) and D-dimer are associated with the development of acute respiratory distress syndrome (ARDS) and an unfavorable clinical course.

3. The third stage of the disease is characterized by fibrotic changes.

Numerous short- and long-term complications involving almost all organ systems have been reported. Data from a prospective, multi-center cohort study in 302 UK healthcare facilities (4) suggests that 49,7% of admitted patients with COVID-19 have at least one in-hospital complication.
The most commonly involved systems were renal (24,3%), respiratory (18,4%), cardiovascular (12,3%), neurological(4,3%) and gastrointestinal (0,8%) (5).

ARDS is seen in up to 15% of patients and is one of the leading causes of death, mainly triggered by elevated levels of pro-inflammatory cytokines, referred to as cytokine storm (CS).

One in-hospital complication seen in critically ill COVID-19 patients with COVID-19-induced pneumonia and ARDS is barotrauma which can be in the form of pneumothorax, pneumomediastinum and subcutaneous emphysema (5,6,7).

Barotrauma has an incidence of 4,2 % in hospitalized patients and ranges from 7,4% to 40% in patients requiring invasive mechanical ventilation and between 4,7% and 8,1% for noninvasive ventilation (7,8,9).

Lung frailty rather than barotrauma is postulated by some authors (10) as leading mechanism in COVID-19 patients with acute respiratory distress syndrome (ARDS), for more cases with pneumomediastinum were observed in patients with ARDS than without (13,6 vs. 1,9%).

There are several mechanisms discussed for this complication (10 - 14):

1. Cytokine-mediated alveolar injury may lead to the release of air which then tracts along the broncho-vascular tree towards the hilus (Macklin effect) thus leading to pneumomediastinum and pneumothorax.
2. Inflammation may lead to alveolar rupture, pneumatocele formation, and also subpleural necrosis leading to the occurence of bronchopleural fistulas.
3. Increased alveolar pressure by coughing and diffuse alveolar injury along with low compliance also make the alveoli more prone to rupture.
4. Ball valve effect due to proximal obstruction by peribronchiolar infiltration.
5. Dexamethasone medication may lead to delay of healing and perpetuating air leakage.
6. Another point is the increased risk for bacterial or fungal co-infection and sepsis in critically ill COVID-19 patients, particularly in case of corticosteroid or interleukin-antagonist medication to cope with hyperinflammation due to „cytokine storm“ or in otherwise immunocompromised patients. 8 % of all patients seem to have bacterial co-infection, with a rise to 72% in hospitalized patients.

So special attention must be paid to symptoms as sudden onset of thoracic pain and dyspnoea in COVID-19 patients potentially indicating spontaneous pneumothorax or pneumomediastinum. The aim of the study is to highlight the rare, but severe complication of barotrauma in COVID-19 pneumonia, discuss possible reasons and emphasize the diagnostic and therapeutic steps to cope with.

5. Methodology:

The literature research was performed using the following Key Words:
COVID-19 – SARS-Cov-2 - Coronavirus infection / diagnostic imaging – ARDS – Invasive Mechanical Ventilation - Barotrauma – Pneumothorax – Pneumomediastinum – Subcutaneous Emphysema - Treatment of pneumothorax in COVID-19 patients – Mechanisms of Pneumothorax development.

Search for Meta-Analysis, Systematic Reviews, prospective studies, retrospective studies, case reports, in Pubmed, Medline, Elsevier Science and Google Scholar with the Key Words, following the published studies and referred reporting. Large retrospective studies were preferred, but some single-case reports were included.

6. Results:

6.1. Epidemiology, Pathophysiology and Cause of Pneumothorax

Pneumothorax represents a common clinical problem (15) and defines the presence of air in the pleural space by:

1. Communication / leak between (broncho)alveolar spaces and pleura,
2. Direct or indirect communication between the atmosphere and the pleural space,
3. Presence of gas-producing organisms in the pleural space.

Clinically pneumothorax is classified as spontaneous (no obvious precipitating factor) and nonspontaneous (Table 1).

Table 1: Clinical classification of pneumothorax

From: Noppen M et al. (15)

Spontaneous	Primary: no apparent underlying lung disease	
	Secondary: Clinically apparent underlying lung disease (e.g. COPD and Cystic Fibrosis)	
	Catamenial: in conjunction with menstruation, probably related to thoracic / pleural endometriosis	
Traumatic	Iatrogenic: Secondary to transthoracic and transbronchial biopsy, central venous catheterisation, pleural biopsy and thoracocentesis, barotrauma (e.g. ventilation-induced)	
	Non-iatrogenic: Secondary to blunt or penetrating chest injury	

Primary Spontaneous Pneumothorax (PSP) Primary spontaneous pneumothorax is defined as the spontaneously occuring presence of air in the pleural space in patients without clinically apparent underlying lung disease.
It typically occurs in tall, thin male subjects, one risk factor is cigarette smoking. It typically occurs at rest, all patients report a sudden ipsilateral chest pain which ususally resolves within 24 hours. Dyspnoea may be present but is usually mild. Rapidly evolving hypotension, tachypnoea, tachycardia and cyanosis should raise the suspicion of tension pneumothorax which is however very rare in PSP.
The etiology is thought to be the formation of apical pleural blebs oder bullae that develop due to increased negative pressure and mechanical alveolar stretch at the apex of the lungs. Pleural porosity, areas of disrupted mesothelial cells at the visceral pleura, replaced by an inflammatory elastofibrotic layer with increased porosity, allowing air leakage into the pleural space is postulated.
The development of blebs, bullae or pleural porosity may be linked to a variety of factors, including distal airway inflammation, hereditary predisposition, anatomical abnormalities of the bronchial tree, ischaemia of the lung apex and others.

Secondary Spontaneous Pneumothorax (SSP): A mulitude of respiratory disorders have been described as an underlying cause. Pneumothorax is rarely an initial manifestation of these diseases and usually presents late in the disease course (Table 2).

Table 2: Diseases related to Secondary Spontaneous Pneumothorax / SSP (Noppen, 15)

Airway disease: COPD/Emphysema, Cystic fibrosis, Severe asthma

Infectious Lung Disease: Viral/Interstitial pneumonia, Necrotising pneumonia, Pneumocystis pneumonia, Tuberculosis

Interstitial Lung Disease: Idiopathic pulmonary fibrosis, Histiocytosis X, Lymphangioleiomatosis

Connective Tissue Disease: Rheumatoid Arthritis (RA), Scleroderma, Ankylosing Spondylitis, Marfan`s Syndrome, Mixed Connective Tissue Disease, etc.

Malignant Disease: Lung Cancer, Sarcoma

The underlying cause of SSP is probably formation of cystic lung changes, as seen in all of the above mentioned diseases (15,16, Table 3).

1. The most important factor of cyst formation is the presence of interstitial abnormality upstream to the site of cyst formation, creating a ball valve effect. These check valves prevent the exit of air on exhalation while allowing air to enter on inspiration.
2. The coexistence of interstitial abnormalisties in a small airways disease may be required for cyst formation. This supposition is supported by the lack of cystic air spaces as a pathologic finding in pure bronchiolitic disorders without peribronchiolar infiltration.
3. Other mechanisms of cyst formation include tract bronchiectasis, alveolar wall dissolution and conflation and local emphysema from collateral air drifts into collapsed acini distal to obstructed bronchioles and barotrauma (mechanical ventilation) (16).

Table 3: Cysts and cyst-like lesions based on the mechanism of cyst formation (excerpt)
from: Boddu P, et al. (16)

Mechanism of cyst formation	Pathophysiology	Associated Diseases	Features
Cystic dilatation of lung structures by peribronchiolar	1. Ball valve effect due to proximal obstruction	Intertsitial Pneumonia, ILD (Interstitial Lung Disease), etc.	Thin-walled (<4mm) infiltration
or alveolar ectasia due to retraction from surrounding fibrosis	2. Traction bronchiolectasis, Collagen vascular disorders Viral bronchiolitis	Honeycombing, associated with indica timg fibrosis	Cysts are
Parenchymal necrosis	Ischemic, inflammatory	Pulmonary infarctions	Thick walls
Alveolar rupture and /or confluence of air spaces	Alveolar dissolution from ischemia or alveolar rupture	COPD Connective Tissue Syndromes	Blebs and Bullae, large cysts due to confluence

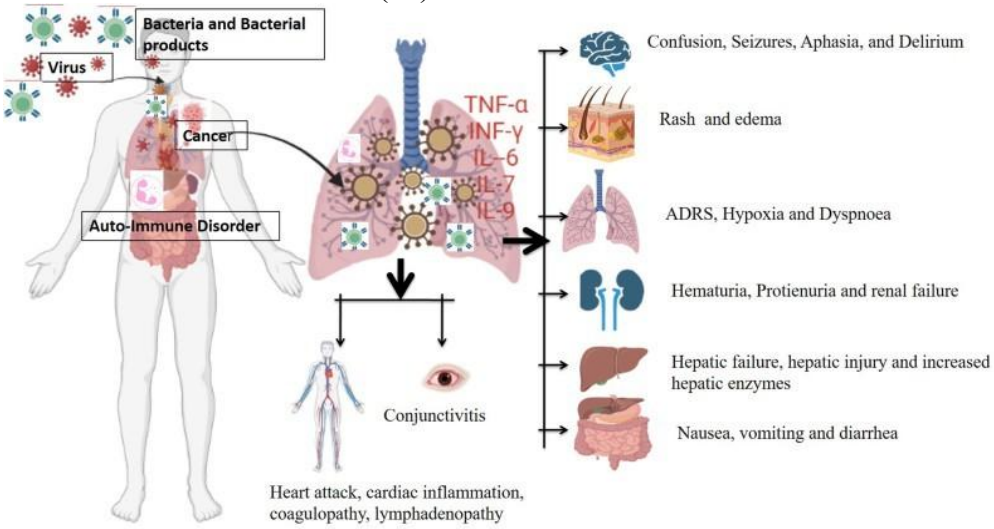
In SSP, dyspnoea is the most prominent clinical feature.

Because lung function in patients with Secondary Spontaneous Pneumothorax is already compromised, this complication often presents as a potentially life-threatening disease, requiring immediate action.
As in PSP, air may enter the pleural space through various mechanisms: direct alveolar rupture (as in ephysema or necrotic pneumonia), via the lung interstitium or backwards via the bronchovascular bundle and mediastinal pleura leading to pneumomediastinum (see Macklin effect: (38 - 41).

6.2. Immunopathogenesis of severe COVID-19

Immunopathogenesis in severe cases of COVID-19 is characterized by systemic hyperinflammation, acute respiratory distress syndrome (ARDS) and multiple organ failure (18 - 22). ARDS as one of the leading causes of death in patients with COVID-19 is mainly triggered by elevated levels of pro-inflammatory cytokines. Interleukins and tumor necrosis factor play a significant role in lung damage in ARDS patients through the impairments of the respiratory epithelium.
This **„Cytokine Storm“ (CS)** (Fig. 1) is a hyperinflammatory state secondary to acute overproduction and uncontrolled release of cytokines by a dysregulated and hyper-activated immune system, locally and systemically.
It manifests clinically as an influenca-like syndrome which can be complicated by multi-organ failure and disseminated coagulopathy leading to death in the most severe cases.
The term cytokine storm was first used to describe the graft-versus-host disease following allogenic stem cell transplantation, then to define the adverse syndromes secondary to the administration of immunostimulating agents and extended to the pathogenesis of many other conditions such as sepsis, viral infections, autoinflannatory disease and others (19, 20). Now it has emerged as a key aspect in the COVID-19 disease as affected patients show high levels of several key proinflammatory cytokines, some of which also correlate with disease severity.

Fig. 1: Clinical manifestation of Cytokine Storm : cytokine storm involves multiple organ failure mediated by hyper-activation of inflammatory pathways. The wide range of clinical abnormalities observed in CS varies from patient to patient based on the severity of the disease. From: Tramboo SR et al. (19).



Activation of immune cells by various virus diseases as SARS-CoV-1, MERS-Cov-1, H1N1 influenza, SARS-CoV-2 (COVID-19), H5N1-influenza, Ebola and others that infect the pulmonary system promotes secretion of a diverse set of cytokines which enhances endothelial-vascular permeability and allows blood cells and fluid to migrate into the alveoli, causing dyspnoea and respiratory failure (19).

Immune hyperactivation occurs occasionally as a consequence of dysregulation or increased amplitude of the immune system (20, 21). In these occasions, feedback mechanisms that would otherwise stop the hyper-inflammation are rendered ineffective which results in overproduction of inflammatory cytokines. Especially in case of COVID-19-induced CS the release of a wide spectrum of pro-inflammatory cytokines both in quantity and quality compared to other forms of CS , there is aggressive manifestation of disease spectrum. It is assumed, that viral entry through ACE-2-receptor and release of the viral RNA and other components result in over-expression of pro-inflammatory cytokines. This impairs the viral clearance and causes a cascade of reactions which further results in the production of more pro-inflammatory cytokines by activation of local pulmonary innate response, the release of Interleukines and TNF (tumor-necrosis factor) induce apoptosis-driven alveolar damage.
Attracted inflammatory cells and immune cells as granulocytes and macrophages damage pulmonary tissue architecture, capillary endothel and alveolae, potentially progressing to Acute Respiratory Distress Syndrome (ARDS), representing the most devastating consequence of CS.

ARDS can be described in 4 Phases (20):

1. Inital / Prodromal Phase: Activation of immune cells in response to viral infection with the production of multiple pro-inflammatory molecules. Lung epithelial cells, pulmonary parenchyma and pulmonary vascular architecture undergo apoptosis, resulting in alveolar edema.
2. Amplification Phase: Excessice Release of pro-inflammatory cytokines: systemic nature of CS and widespread inflammation and tissue damage, resulting in disruption of endothelial cell function, coagulation abnormalities, microvascular permeability alterations, hemorrhages and thrombosis.
3. Organ Dysfunction Phase: life-threatening complications. Recruitment of fibroblasts in pulmonary tissue, fibrin deposition and alveolar collapse.
4. Resolution Phase: Anti-inflammatory and immune modulatory mechanisms

6.3. Histologic findings in the lung of COVID-19 patients:

The overproduction of early response proinflammatory cytokines results in what has been described as cytokine storm, leading to vascular hyperpermeability and activation of coagulation pathways with the result of possible multiorganic failure and eventually death, on the other hand an adequate inflammatory response is crucial for pathogen clearance.

The lungs from COVID-19-patients show significant pathological lesions, including alveolar exudative and interstitial inflammation, alveolar epithelium proliferation and hyaline membrane formation. While COVID-19 is mainly distributed to the lung, the infection also involves damages of heart, vessels, liver, kindneys and other organs.

At post-mortem macroscopic examination (22), acute pulmonary edema was identified in 70% of the autopsied cases (Figure 2). The lung increased in weight, the consistency was firmer and had a particular appearance: reddish-brown to purple in color due to „hepatization“.
Secondary bronchopneumonia with purulent and hemorrhagic secretions can be seen.

The most reported microscopic finding in acute COVID-19 lung (Table 4) is diffuse alveolar damage (DAD) in the lung histology, leading to acute respiratory distress syndrome (ARDS) in some patients. Hyaline membranes, hyperplasia of type II-pneumocytes, the presence of inflammation cells as lymphocytes, macrophages and multilineated giant cells were common.

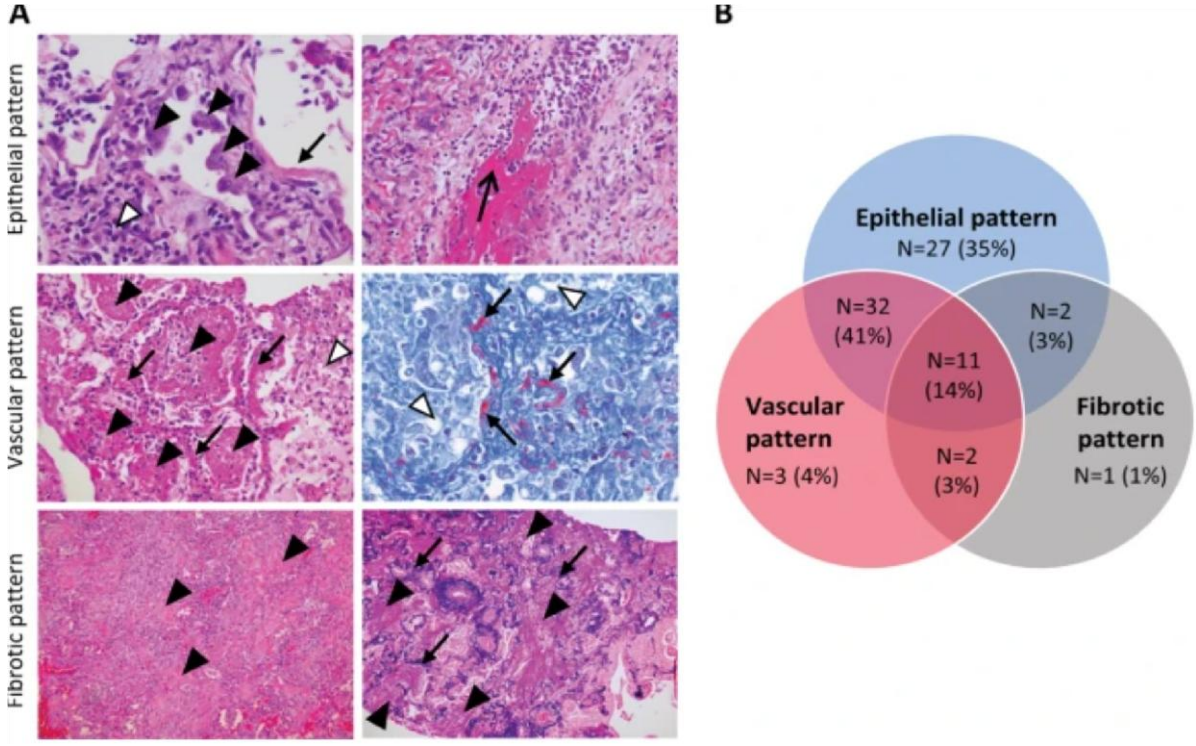
COVID-19 can cause venous and arterial thrombotic complications through a combination of thrombocytopenia, prolonged prothrombin time and elevated D-dimer, likely due to disseminated intravascular coagulation or thrombotic microangiopathy in the lung (22, 23).

Table 4: Overview of Pulmonary Pathology Findings in COVID-19 (n = 129).
From Milross, et al. (22)

Pathological characteristics	**Number of cases: 129 / %**
Epithelial	110 (85%)
Diffuse alveolar damage (DAD) and / or hyaline membranes	97 (75%)
Desquamation and / or reactive hyperplasia of pneumocytes	93 (72%)
Sqamous metaplasia of alveolar epithellium	25 (19%)
Multilineated giant cells	26 (20%)
Viral cytopathic changes, particels and / or inclusion bodies	26 (20%)
Intra-alveolar fibrous plugs	2 (2%)
Vascular	76 (59%)
Capillary congestion	58 (45%)
(Micro)thrombi	50 (39%)
Alveolar hemorrhage	42 (33%)
Alveolar proteinosis	31 (24%)
Intra-alveolar fibrinous exudates and / or fibrin deposition (features of acute fibrinous and organizing pneumonia)	34 (26%)
Capillary changes (i.e. proliferation or thickening, fibrin deposition and endothelial cell detachment or cell-death)	32 (25%)
Peri- or intravascular inflammatory infiltrate	12 (9%)
Fibrotic	28 (22%)
Interstitial fibrous changes (i.e. fibroblast hyperplasia, fibrosis, septal collagen deposition)	43 (33%)
Microcystic honeycombing	9 (7%)
Other	

Interstitial and / or intra-alveolar inflammatory infiltrate	82 (64%)
Interstitial and intra-alveolar edema	59 (46%)

Fig. 2: Summary of cases with the epithelial, vascular and / or fibrotic pattern of lung injury
From: Polak SB et al. (3).



A. Example of images of lung sections showing epithelial (top; hematoxylin-eosin stains), vascular (middle; left hematoxylin-eosin stain, right fibrin-Lendrim (MSB) stain) and fibrotic (bottom; left hematoxylin-eosin stain, right Verhoeff-van Gieson stain) pattern of lung injury in COVID-19. In the top panels, atypia and detachment of type-II pneumocytes (closed arrowheads), hyaline membrane formation (closed arrow), imterstitial inflammatory response (open arrowhead) and denudation of bronchial epithelium (open arrow) are indicated. In the middle panels, intracapillary hyaline thrombi (arrows), acute fibrinous and organizing pneumonia (closed arrowheads) and edema (open arrowhead) are indicated, possibly representing fibrosing organizing pneumonia. Images were obtained from autopsies of 78 COVID-19 patients performed at the Erasmus Medical Center.

B. Venn diagram summarizing the histological patterns of lung injury in 78 COVID-19 patients.

The histopathological picture of COVID-19-related pneumonitis appears to encompass epithelial, vascular and fibrotic patterns of lung injury.
By analyzing these patterns in patients in different stages of disease relative to the onset of symptoms, a **timeline** (Fig. 3) can be identified.

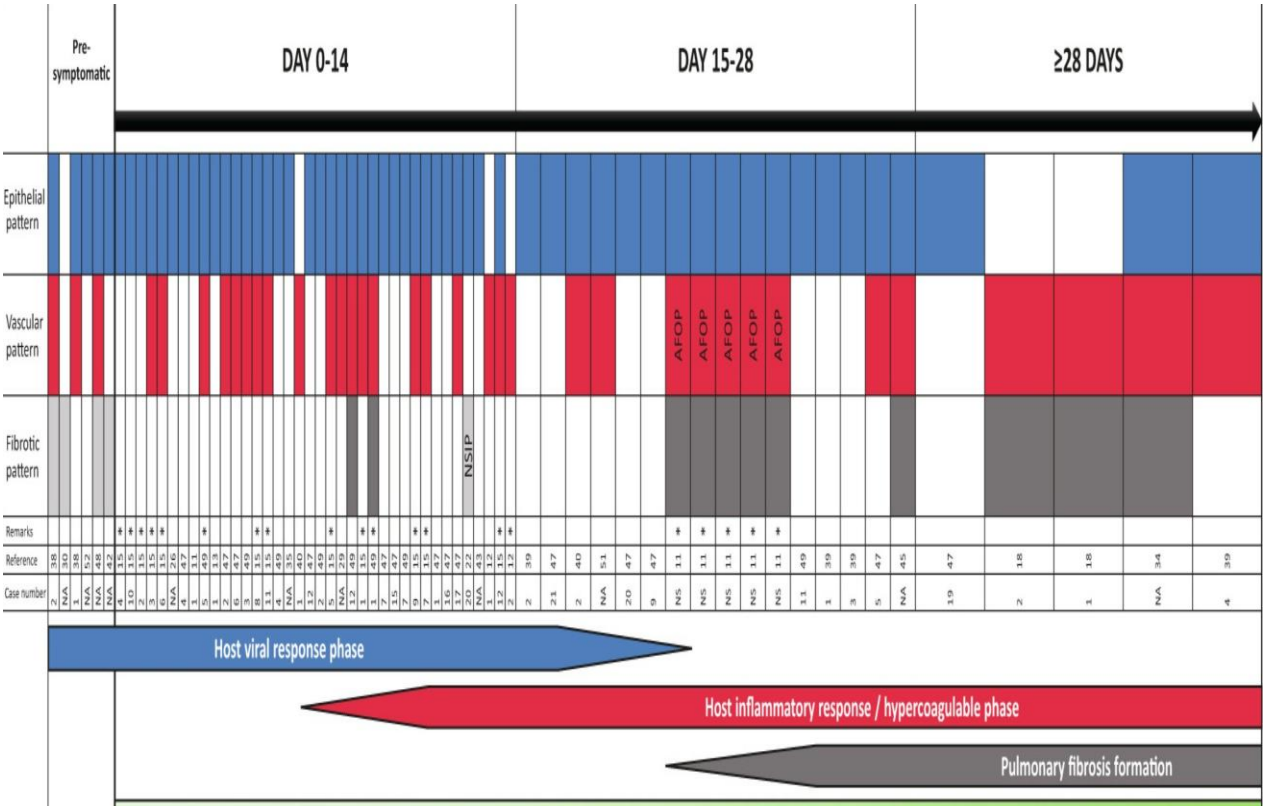
1. Epithelial changes – including DAD, denudation and reactive pneumocyte atypia – were present in all stages of the disease.

2. Vascular changes, including microvascular damage, thrombi, intra-alveolar fibrin deposits and other features of acute fibrinous and organizing pneumonia – also occured during the early phases. This vascular pattern of COVID-19 lung injury is prominent, when compared with other forms of ARDS and is in line with clinical studies reporting an impressive 49% of bases with thrombotic events. ARDS can be frequently complicated by vascular obstructions,

microthrombosis and vasoconstriction in pulmonary vessels, leading to pulmonary hypertension. The prevalence of pulmonary hypertension in patients with COVID-19 is about 12 % (23).

3. Fibrotic changes generally appeared about 3 weeks after the onset of symptoms (few patients had fibrosis at an early stage, likely due to pre-existing lung disease).

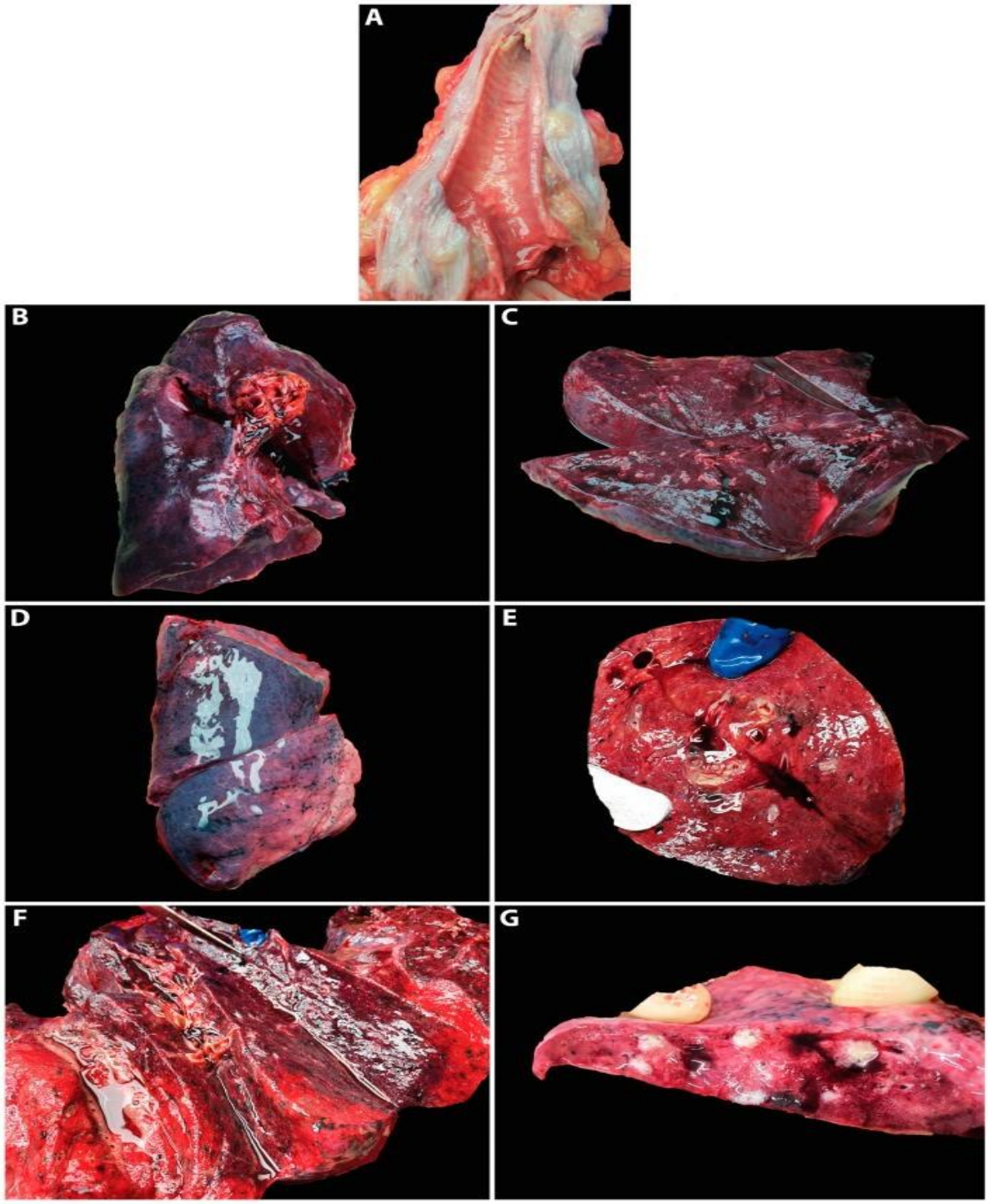
Fig. 3: Timeline correlating the epithelial, vascular and fibrotic patterns of lung injury with the duration of COVID-19 symptoms. From: Polak SB, et al. (3)



Shown are the identified histological pulmonary patterns (epithelial, vascular and fibrotic) for 65 individual cases; each case is shown in a single column. Cases are organized chronologically in four time periods: the number of days since the onset of symptoms is indicated.
For the fibrotic pattern cases shaded in light gray are cases in which fibrotic changes were likely pre-existing and were not associated with COVID-19, cases in dark gray indicate fibrotic changes following COVID-19 infection. For cases indicated with an asterisk (*), the duration of the clinical course was estimated from a report with aggregated pathological findings. Shown below the timeline is the approximate occurence of COVID-19 clinical phases, color-code based on the three patterns of histological pulmonary changes and the transition of respiratory phenotypes.

The post-mortem macroscopic aspects (3) of patients died of COVID-19 pneumonia / ARDS show massive pulmonary edema, hemorrhage and foamy liquid in the bronchi and trachea, in case of secondary bronchopneumonia multiple purulent foci (Fig. 4)

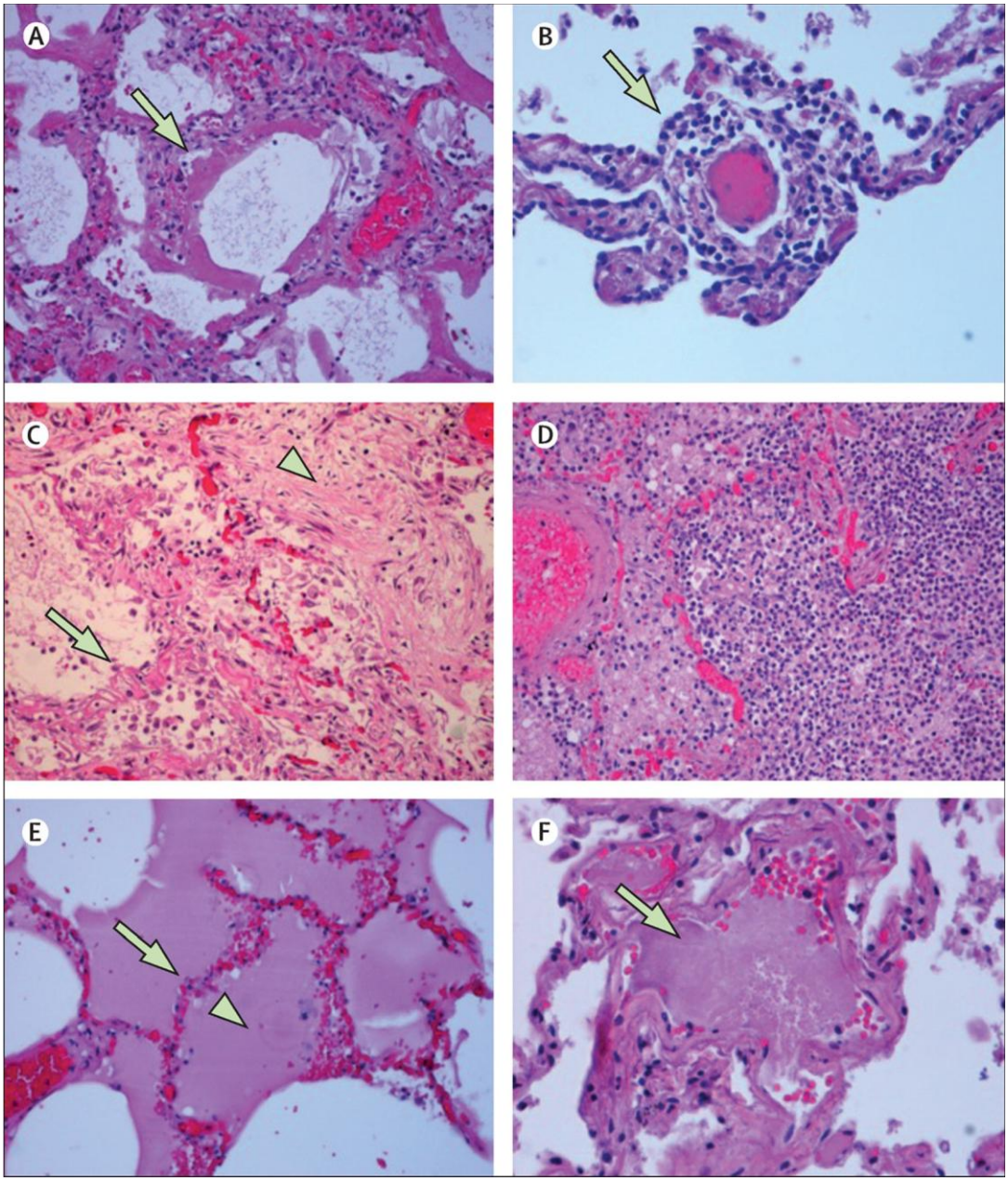
Fig. 4: Macroscopic post-mortem aspects of lung infected with SARS-COV-1 Delta variant: From: Polak SB et al. (3)



A: acute pulmonary edema, foamy liquid in trachea
B-F: condensed, violaceous lung
G: expression of pulmonary section in secondary bronchopneumonia, purulent foci

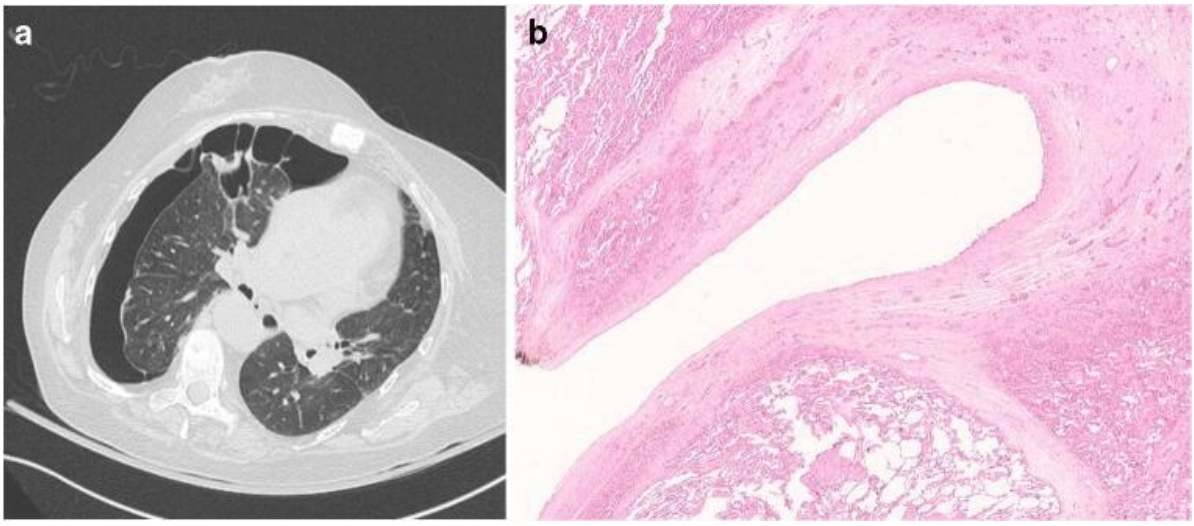
Microscopic examinations of lung tissue in severely affected COVID-19 patients reveal extensive alveolar edema, fibroblast infiltration, fibrin deposition and lymphocytic infiltration (Fig. 5), development of cystic lung lesions (24) (Fig. 6) and fibrosis (Fig. 7).

Fig 5: Histopathological findings in acute COVID-19, Haematoxylin and eosin staining of post-mortem lung sections from patients who died with COVID-19. From: Jeican II (2)



(A) Exudative diffuse alveolar disease featuring prominent hyaline membranes (arrow) with interstitial infiltration by mononuclear cells, alveolar wall congestion and cellular debris.
(B) Perivascular lymphocytic infiltrate (arrow).
(C) Organizing diffuse alveolar disease with myofibroblast proliferation (arrowhead), fibrinous exudates, hyaline membrane remnants (arrow) and substantial alveolar architectural disruption.
(D) Acute bronchopneumonia featuring prominent intra-alveolar neutrophilic infiltration. (E) Pulmonary edema, characterized by eosinophilic fluid within the alveolar airspace (arrowhead), alveolar wall congestion (arrow) and absence of cellular damage. (F) Platelet-rich thrombus (arrow) causing expansion of an intra-acinar vessel.

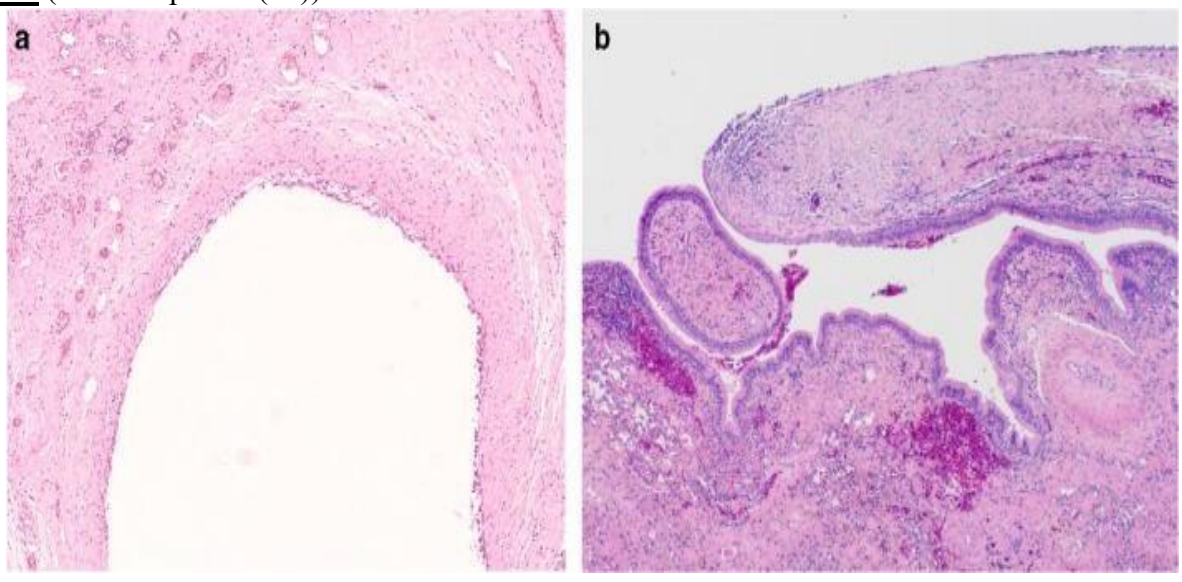
Fig. 6 /7: Histopathological findings in a case of cystic lung lesion and pneumothorax in COVID-19 (From: Capleton (24).



a. Axial CT image demonstrates a right-sided pneumothorax with a cystic lesion in the peripheral lung parenchyma wich shows communication with the pleural space, compatible with pneumatocele.

b. Low power view of the cystic space after resection demonstrating the densely fibrotic wall with surrounding vascular congestion.

Fig. 7: (From Capleton (24))



a. Background lung showing septal fibrosis with edema and vascular congestion with alternating areas of aerated and collapsed lung

b. High power view showing intra-alveolar fibrin and a fibromyxoid plug with focal haemosiderin deposition.

6.4. Typical radiological findings in COVID-19

According to the Radiologic Society of North America (RSNA, 25),

1. Imaging is not indicated in patients suspected of having COVID-19 and mild clinical features unless they are at risk for disease progression.
2. Imaging is indicated in a patient with COVID-19 and worsening respiratory status. 3. In a resource-constrained environment, imaging is indicated for medical triage of patients suspected of having COVID-19 who present with moderate to severe clinical features and a high pretest probability of disease.
4. Daily chest radiographs are not indicated in stable intubated patients.
5. CT is indicated in a patient with functional impairment and / or hypoxemia after recovery from COVID-19.

6.4.1 Chest X-Ray

Chest radiography is often the first imaging modality of choice for patients with known or suspected COVID-19 pneumonia (25). In the literature, the diagnostic value of chest X-ray is reported to vary between 30% and 60%, which is relatively low. Although it is possible to detect some abnormalities in the presence of viral pneumonia, normal findings obtained from this modality do not exclude the disease, the early stages Chest X-rays often do not show any abnormality.
However, in mild COVID-19 conditions, it may demonstrate local irregular (ground glass) opacities in the outer parts of the lung and in the subpleural region (Fig. 8). Lung involvement occurs typical in bilateral involvement of the peripheral and lower lobe basal segments. In severe cases, there is a widespread, sometimes patchy multiple consolidations (Fig. 9). Pneumothorax, lung collapse and subcutaneous emphysema are detected, but a small pneumothorax may be difficult to detect in supine or prone position in the ICU (Fig. 10). In conclusion, the diagnostic contribution of chest X-ray is lower than that of chest CT.

Fig. 8: Early stage of COVID-19 pneumonia with ground glass opacities in a predominantly peripheral and basal distribution. Male patient, 30 y (Radiopaedia, by Salah Aljilly).

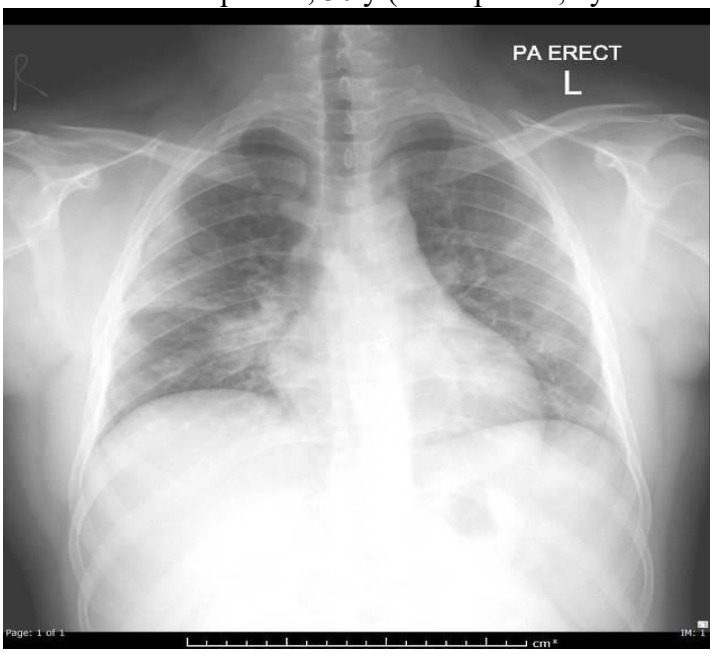


Fig. 9: Progressive COVID-19 pneumonia with bilateral ground-glass opacicities affecting both lungs, more prominent in the upper lobes and paramediastinal parenchyma. The patient is intubated and has a central venous line. Male patient, 75 y (Radiopaedia, Case distributed by Anton Aubanell Creus)

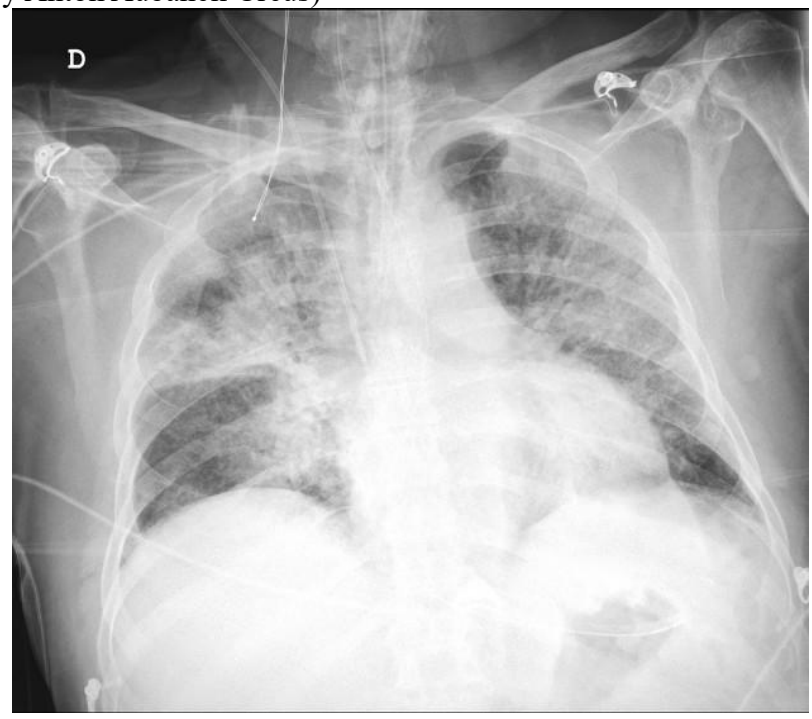
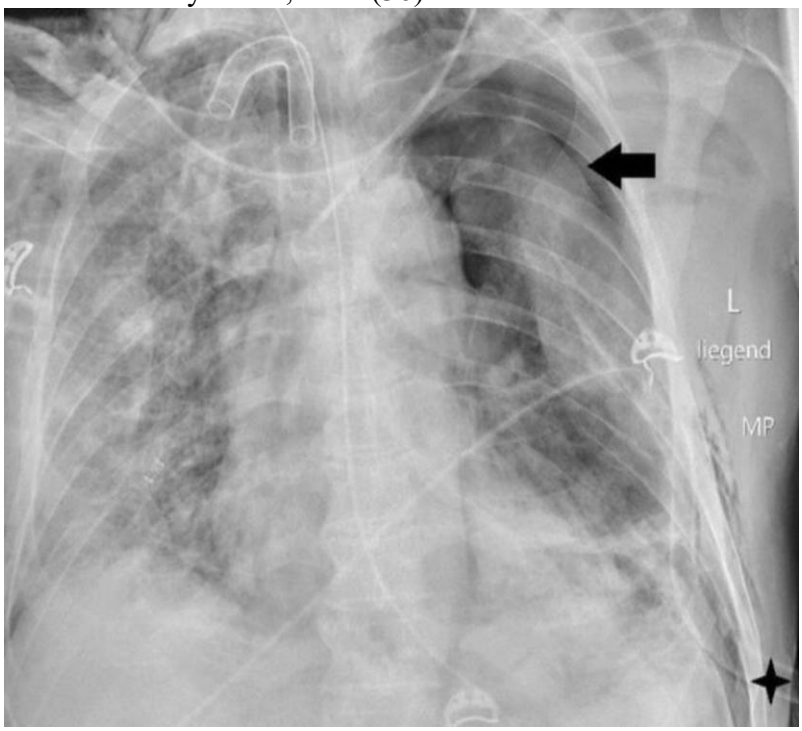


Fig. 10: Left-sided pneumothorax and partial collapse of the left lung (black arrow) and subcutaneous emphysema / emphysema of the chest wall (asterisk) in a patient with severe COVID-19 pneumonia. From: Mykoliuk, et al. (36)



6.4.2 Chest-CT

It is sensitive in the early signs of COVID-19 and changes that may not be seen in Chest X-ray, but about 50% of chest CT may be normal in early stage. During active infection, chest CT can help to monitor the course of the disease and provide timely treatment.
CT is showing high sensitivity (97%) but poor specificity (25%) for the diagnosis of COVID-19, as the findings overlap those of other viral types of pneumonia. However, some findings may be useful in the differential diagnosis.
A systematic literature research (26, 27) showed characteristic patterns and distribution of CT manifestations of COVID-19 pneumonia: Ground Glass Opacicities (GGO), bilateral involvement, peripheral distribution and multilobar involvement (Table 5).

Table 5: Common Patterns and Distrubution in Inital CT Images of 919 Patients with COVID-19 Disease. From: Salehi S, et al. (27).

Imaging Finding	No. of Studies	No. (%) of Reported Cases/Total No. of Patients
Bilateral involvement	12	435/497 (87.5)
Peripheral distribution	12	92/121 (76.0)
Posterior involvement	1	41/51 (80.4)
Multilobar involvement	5	108/137 (78.8)
Ground-glass opacification	22	346/393 (88.0)
Consolidation	10	65/204 (31.8)

Beneath GGOs, other CT findings included interstitial / interlobular septal thickening, bronchiectasis, pleural thickening and subpleural involvement, mainly in the later stages of the disease with various rates across the studies.
Pleural or pericardial effusion, lymphadenopathy, cavitation, CT halo sign and pneumothorax were less common, however even small pneumothorax is clearly visible on CT.

CT findings according to the stage of the disease (27):

1. During the ultra-early stage (asymptomatic, 1-2 weeks after exposure), CT may show single or multiple GGO, patchy consolidative opacities, pulmonary nodules encircled by GGO and air bronchograms.
2. In the early stage (early symptomatic presentation), CT-findings inculde single or multiple GGOs or GGO combined with interlobular septal thickening.
3. In the rapid progession stage (days 3 – 7 of symptomatic presentation), CT findings include large, light consolidative opacities and air bronchograms.
4. During the consolidation stage (second week of symptomatic presentation), reduction in density and size of the consolidative opacities may be seen.
5. About 2 – 3 weeks after onset, CT may show dispersed patchy consolidative opacities, bronchial wall thickening and interlobar septal thickening.

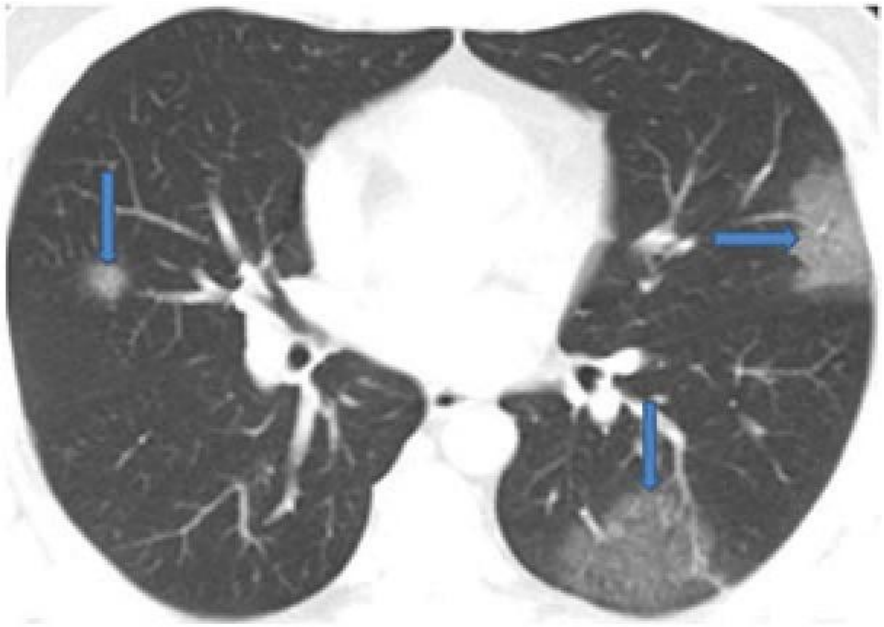
In average, most patients show an increase of GGOs, number of involved lobes, intensification of „crazy paving pattern“ and appearance of consolidative opacities over time. CT findings were most prominent around day 10 of the disease.

After 14 days, improvement in imaging findings was reported in 75% of the patients, incuding decreased number of involved lobes, resolution of „crazy paving pattern“ and consolidations (28, 29).

The hallmark of COVID-19 is the bilateral presence of patchy ground glass opacities (GGO) that can merge into dense, consolidative lesions with a perdominantly peripheral distribution in the subpleural areas, as well as bronchovascular bundles. As disease progresses, the number of lesions can rapidly increase and extend into central regions.
During the recovery, lesions gradually regress over two weeks, during which time fibrotic changes may occur.

Ground glass opacities (GGO) are nonspecific findings defined as hazy lung opacities that do not cover the underlying vascular or bronchial boundaries and are assumed to be related to partial airspace filling or interstitial thickening (30, see Fig. 11). GGOs are seen at a rate of 50% to 95%, may bei accompanied by consolidations in varying degrees, depending on the stage of disease.

Fig. 11: 35-year old male COVID-19 patient presenting fever and headache for 4 days. CT -scan shows pure **ground-glass opacities (GGO)** in bilateral multilobe distribution (arrows).
From: Karacan A et al. (28).



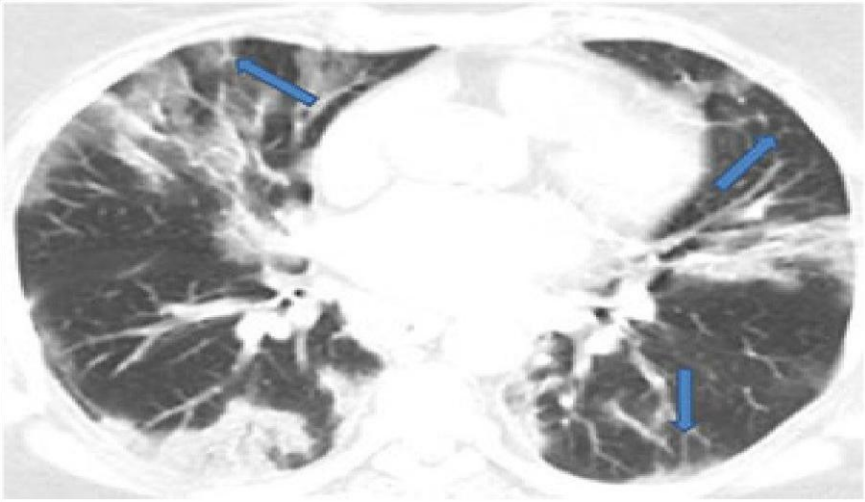
Consolidations (see Fig 12) have been reported in 20% - 63% of cases and result from the complete displacement of alveolar air spaces by pathological fluids or cells, leading to an increase in parenchymal density that obscures the underlying vessels and bronchial walls. They occur with the progression of the disease, may be multifocal, irregular or segmental with subpleural or peribronchovascular distribution and often accompany GGOs.

Reticular patterns (see Fig. 12) consist of a complex network of linear opacities associated with **interlobular and intralobular septal thickening** and is caused by lymphocyte infiltration. With an incidence of about 27% it is the third most common finding in COVID-19 and its incidence increases over the course of the disease.

Airway changes as bronchiectasis is a consequence of bronchi filled with mucus of high viscosity, bronchial obstruction and inflammatory damage to the bronchial wall that can lead to destruction of the bronchial wall structure and development of fibrosis.
Air bronchograms, in which air-filled bronchi can be seen in attenuated background is an unspecific finding.

Pleural thickening can be seen in 32% of cases, The presence of pleural effusion is rare (5%) but seems to be a poor prognostic factor.

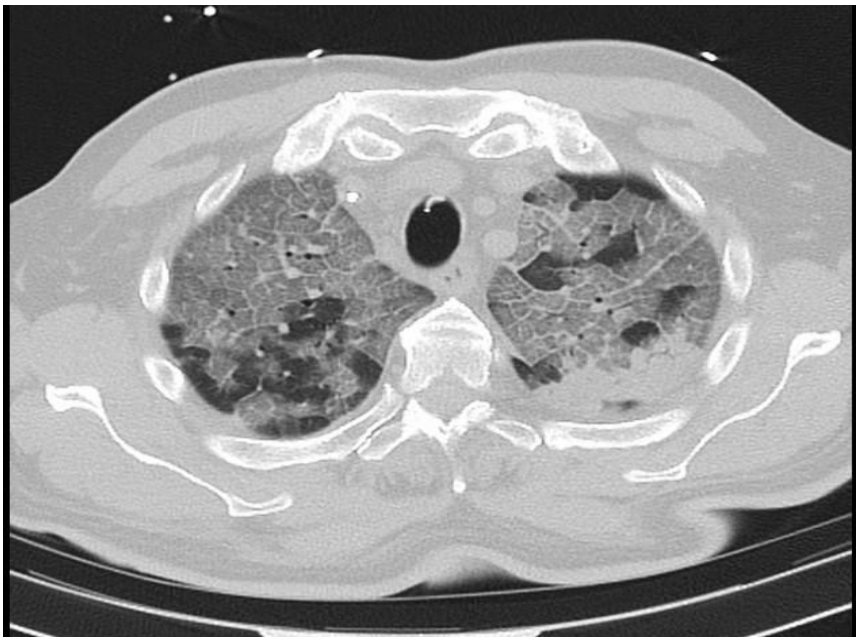
Fig. 12: 66-year-old male COVID-19 patient presenting fever with cough for 7 days. Multiple **ground-glass-opacities** (GGO) and **consolidatons** with **thickened intralobular and** interlobular septum (arrows) (28)



Crazy paving pattern (Fig.13, 14) is not specific for COVID-19 pneumonia and defined as the presence of GGOs with overlapping interlobular septal thickening, giving the appearence of irregular cobblestones and may be associated with alveolar edema combined with interstitial inflammation (26 - 30). In COVID-19 it is seen less frequent than in other diseases (i.e. Pulmonary edema, ARDS, bacterial pneumonia and others) in about 5% - 36% of patients and may be considered an indication of progression.

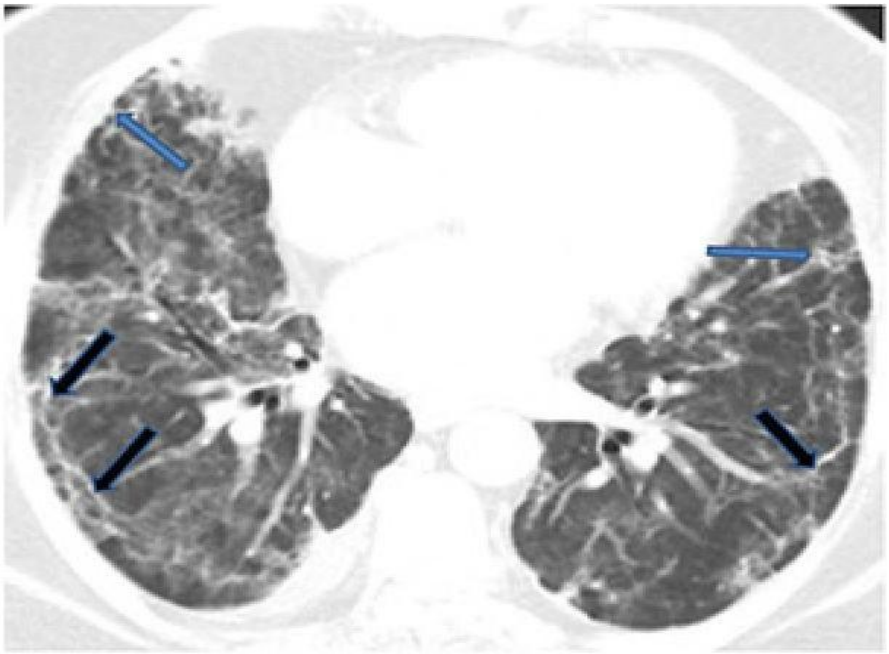
Fig. 13: Irregular („crazy“) paving pattern

Fig. 14: **Crazy paving pattern** in a patient with COVID-19 pneumonia (29).



Subpleural lines (Fig. 15) as a nonsspecific sign are seen in 33% of COVID-19 cases and refer to thin curvilinear opacities of approximately 1 – 3 mm in thickness, located in the subpleural region and distributed parallel to the pleural surface (Fig. 12) and may be associated with the predominantly peripheral location of parenchymal changes in COVID-19 (Chung M et al.,29).

Fig. 15: 49-year old female COVID-19 patient presenting chest pain for 14 days. **Subpleural lines** (black arrows) with **thickened intralobular and interlobular septa** (blue arrows) (29)



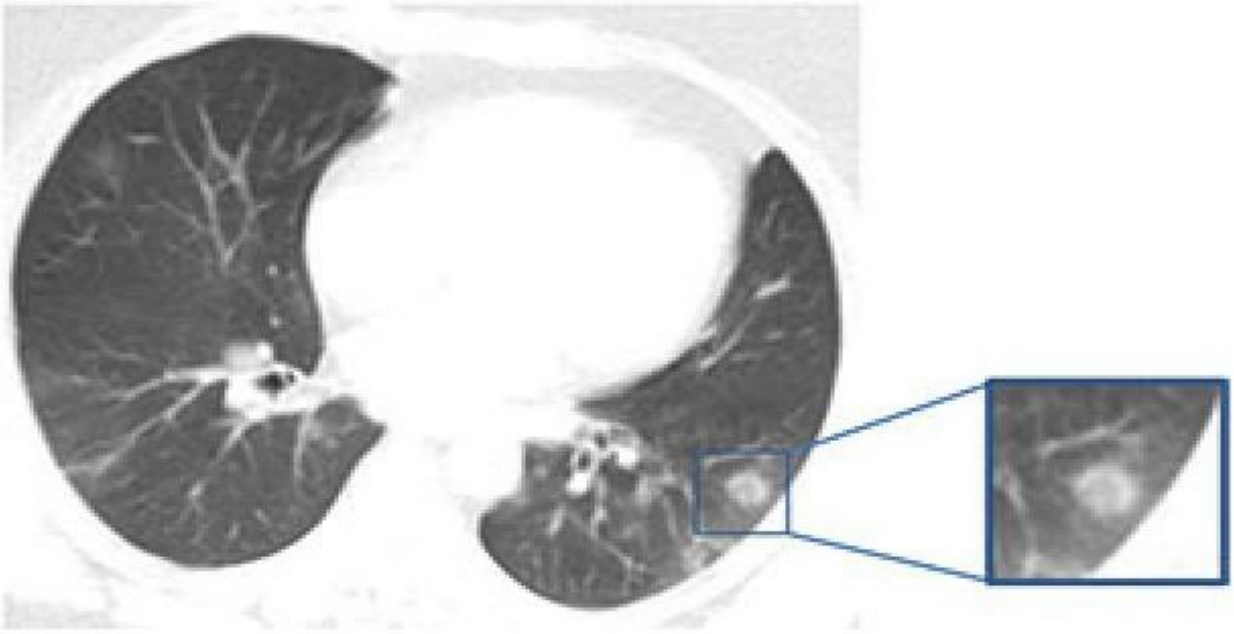
Fibrotic lesions may occur in patients with proliferative disease and those recovering from chronic pulmonary inflammation due to the replacement of cellular components by scar tissue. Fibrosis is usually seen at two to three weeks after onset of COVID when interstitial changes begin to occur. The general belief is that fibrosis is a part of the recovery process.

Pulmonary nodules are often associated with viral pneumonia (29) and are found in 3% - 13% of patients, sometimes accompanied by a halo sign.

The Halo Sign (28, 29) is described as a nodule or mass surrounded by GGOs. The underlying pathological mechanisms is probably hemorrhage and it can be seen as well in other pulmonary infections, organizing pneumonia and in hypervascular metastases.

The Reversed Halo Sign (29, Fig. 16) is also not specific for COVID-19 and a ring-like consolidation zone with an overlapping circular GGO. It is considered as a healing lesion with a low-density core or a new lesion that develops around a preexisting GGO.

Fig. 16: 48-year old male COVID-19 patient presenting fever for 5 days. CT scan shows a **reversed halo sign** (central grund-glass opacity surrounded by denser consolidation of crescentic shape) in left lower lobe (frame), (29)

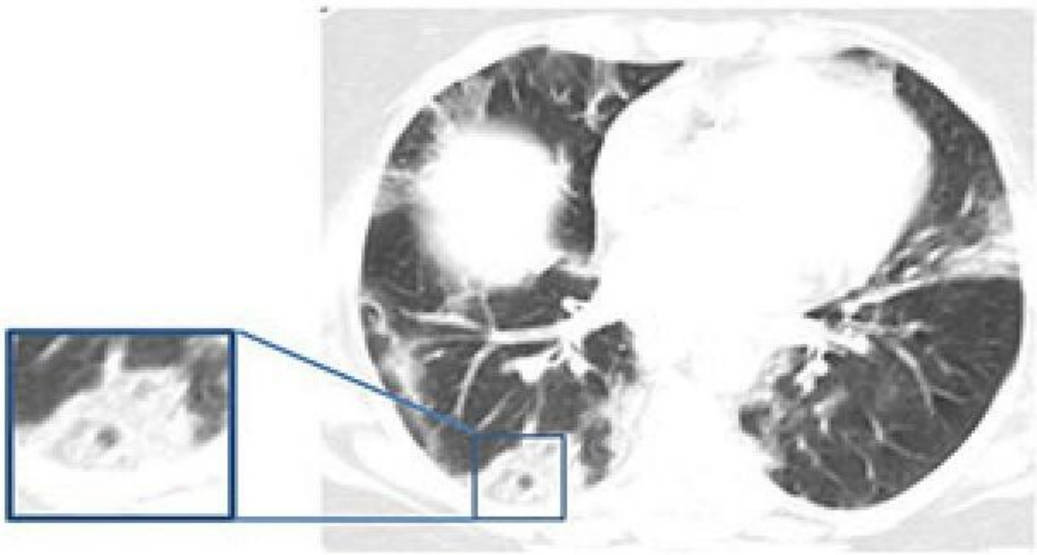


Vascular changes can be caused by proinflammatory factors resulting in capillary wall damage and edema and show dilatation of pulmonary vessels.

Lymphadenopathy with the short-axis diameter of the mediastinal lymph node is more than 1 cm, has been reported in 4% - 8% and is considered to be an essential risk factor for severe pneumonia. However, bacterial superinfection should be suspected when accompanied by pleural effusion and small lung nodules.

Cavitation and Air Bubble Sign (29) are rare in COVID-19, defined as small air-containing areas associated with bronchiolectasis (Fig. 17).
Bubbles and blebs may expand to cystic pulmonary lesions (30, 31) and so become the predisposing factor of pneumothorax.

Fig. 17: 49-year old male COVID-19 patient presenting fever with diarrhea for 3 days.
Air bubble sign (frame) with GGO and consolidation in the right inferior lobe (29).



Pneumothorax and Pneumomediastinum (see Fig. 18-20) in COVID-19 patients is a rare event of 1% in hospitalized patients, 3% with pneumonia and 6% in mechanically ventilated patients (39, 31), but can also happen in complete asymptomatic patients or patients with only mild symptoms and even after recovery from acute phase of COVID-19 (31).

A sudden onset of chest pain and shortness of breath may be observed.
COVID-19 pneumonia may cause cystic features of lung parenchyma which can resolve or progress to larger blebs. Potential causes include the high airway pressure by respiratory support in mechanical ventilated patients as well as spontaneous rupture of fragile small airways.
Patients with extensive lung damage and protracted clinical course are more likely to experience pneumothorax, so it is recognized as a poor prognostic characteristic and prompt diagnosis and management might decrease the morbidity and mortality.

Besides COVID-19-induced lung damage, barotrauma by mechanically ventilated patients and also increased thoracic pressure caused by frequent and heavy coughing could be one of the explanations for the development of barotrauma complications (33 - 38).

Fig. 18: CT-scan of patient diagnosed with COVID-19, pneumothorax and bulla.

Axial and coromal plane of CT thorax showing a moderate right-sided pneumothorax (black arrow) and large air containing bulla in the right middle lobe (red arrow). The mediatinal structures are shifted to the left with mild pneumomediastinum noted (blue arrow) from: Al Shokri et al (36).

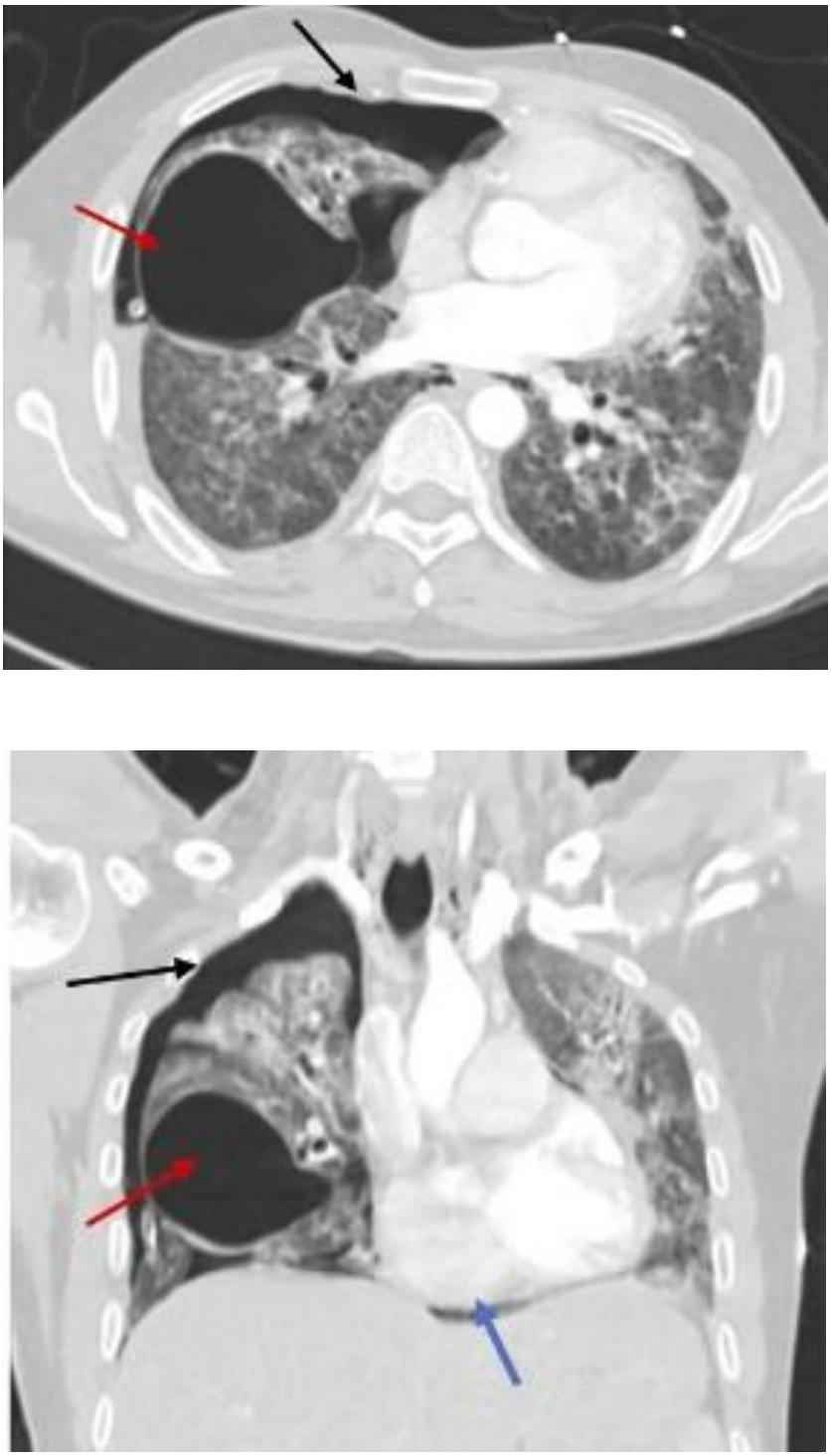


Fig. 19: 38-year-old man diagnosed with severe COVID-19-pneumonia.

A: The primary CT scan showed bilateral, patchy GGOs with co-existing consolidations. B: 9 days later, a follw-up CT scan showed multiple cysts in the GGOs (bilaterally) and a left pneumothorax. The cysts featured a smooth inner wall, the maximum diameter was about 5 cm. C: The third CT scan (performed 5 days later) showed that the left pneumothorax and a small cyst on the left pulmonary margin had disappeared; the remaining cysts reduced in size slightly.

From: Liu K, et al. (31)

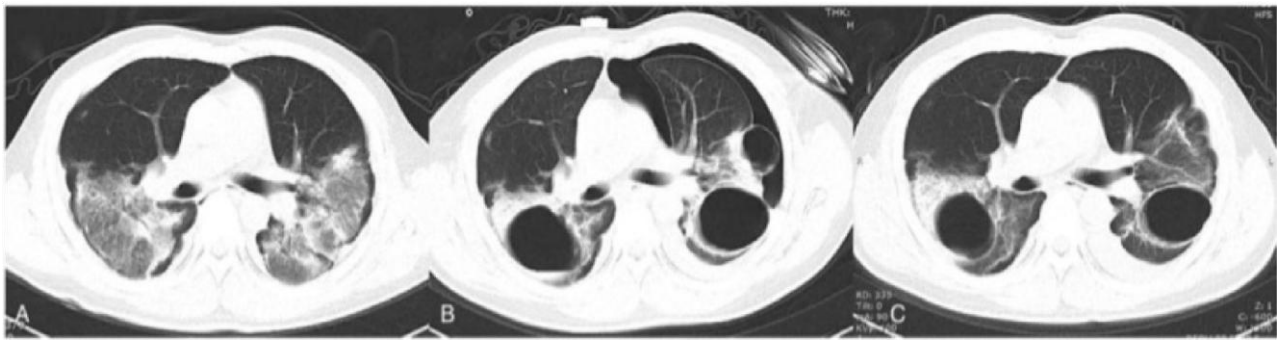


Fig. 20: CT scans of 38-year old man who presented with COVID-19 (From Sun R, et al. 38).

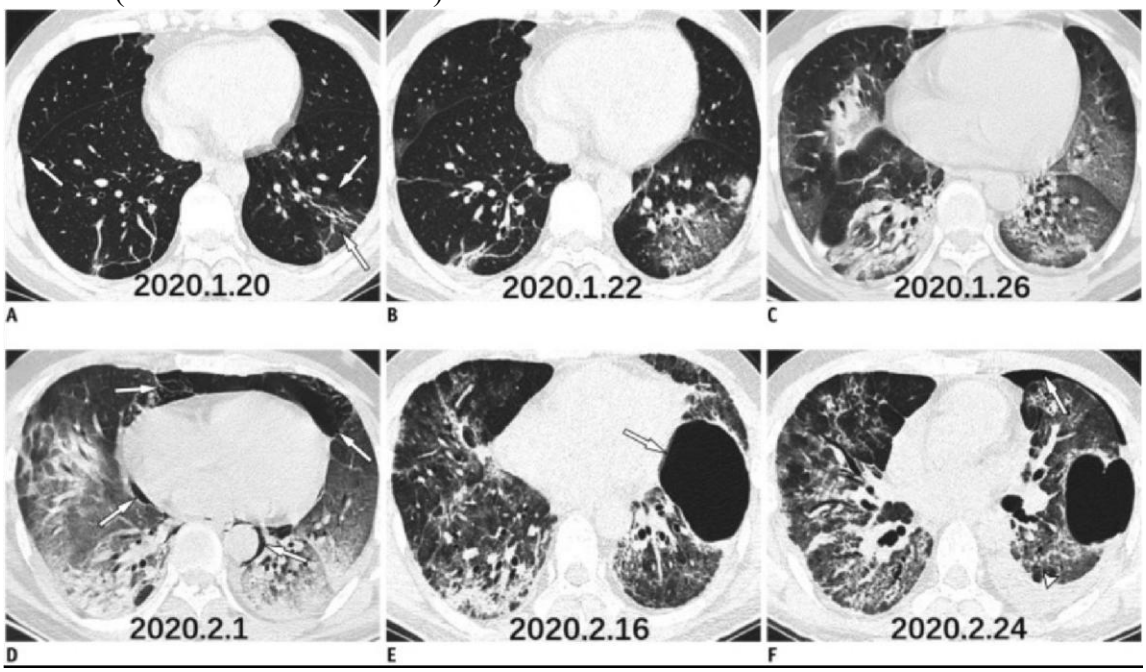
A. Chest CT scan shows multifocal GGO along bronchovascular bundles and subpleural areas (arrows).

B,C. CT scans obtained on day 3 and 7 show a rapid progressions of GGO and consolidation in both lower lung zones.

D. CT scan obtained on day 11 shows bilateral subpleural consolidation and mediastinal emphysema (arrows).

E. CT chest scan obtained on day 26 shows improvement of pulmonary lesions and mediastinal emphysema; however, a giant bulla (arrow) is noted in left lung.

F. Final follw-up CT scan obtained on day 34 shows pneumothorax (arrow) and pleural effusion (arrowhead in left thorax).



6.5 Mechanisms of Pneumothorax buildup in COVID-19:

6.5.1 The Macklin Effect

In 1939 Charles Macklin (39) first studied the pathophysiology of spontaneous pneumomediastinum (SPM) through experimental works. The release of air into the interstitium secondary to acini rupture causes distension of the secondary pulmonary lobule.
As this progresses, the air dissects the arteriobronchial sheath until reaching the pulmonary hilus entering the mediastinal compartment (Fig. 21 – 24).
Three mechanisms are described (39):

1. Rupture of alveolar acini.
2. Mucosal barrier disruption (tracheobronchial tree) allows unrestrained air passage towards the mediastinum.
3. Gas produced by microorganisms in the mediastinum or adjacent areas.

Aetologies are varied: infection, trauma, iatrogenic or without apparent explanation (spontaneous).

Fig. 21: Macklin Effect suggests that the air leak caused by alveolar rupture spreads along the bronchovascular sheath to the mediastinum and then to the subcutaneous tissue along the path of least resistance. Some air may enter the pleural space after rupture of mediastinal pleura. From: Radiopaedia, Hsu C et al. (41).

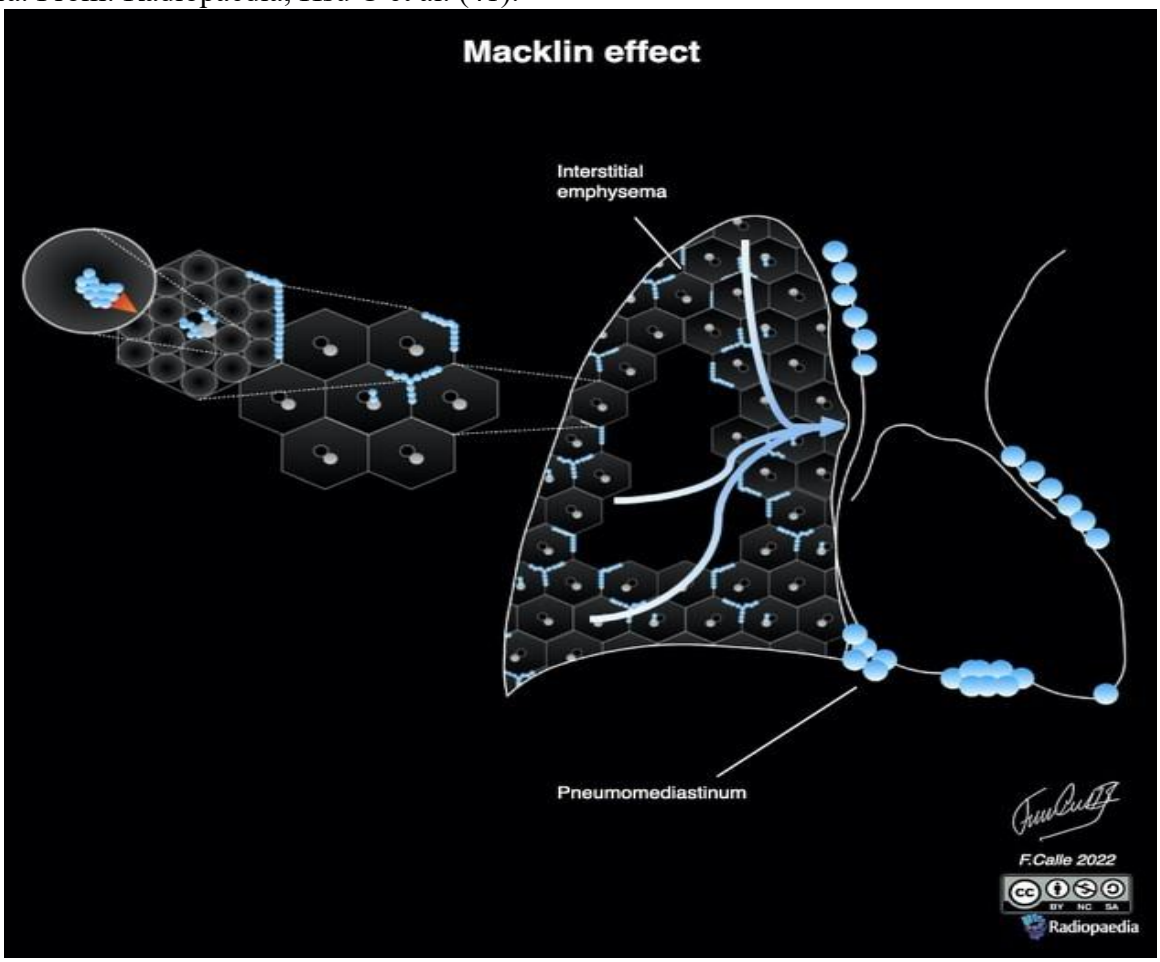
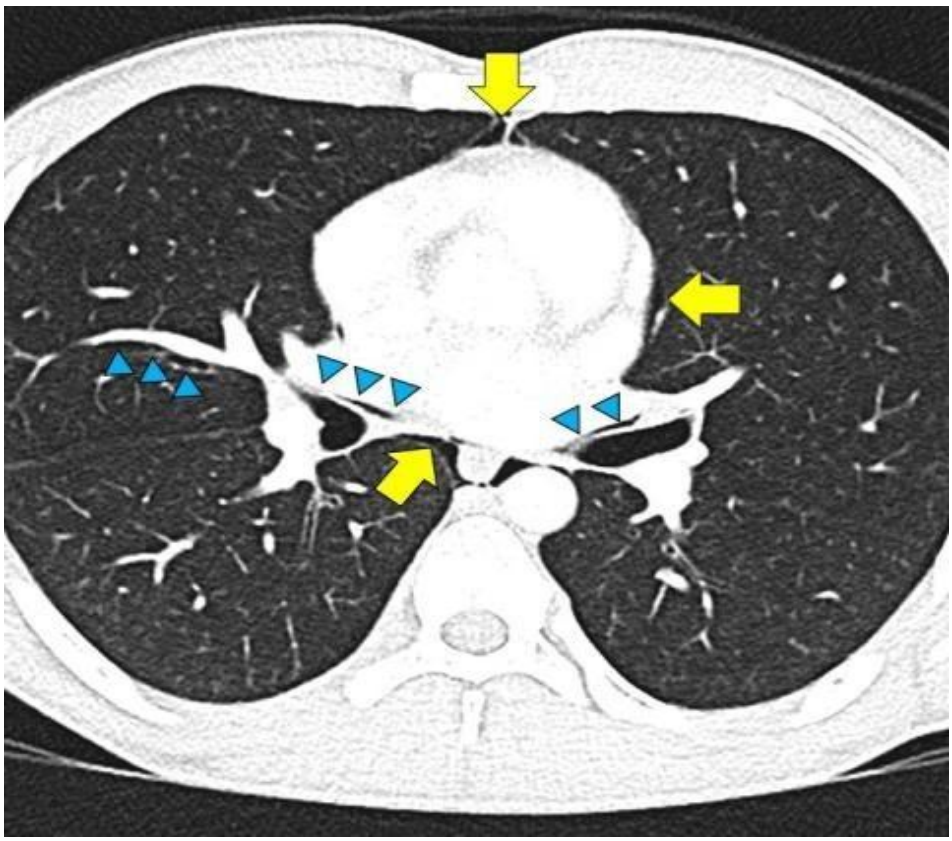


Fig. 22: **CT Thorax** shows linear air bands along the bronchovascular sheaths (blue arrowheads), pneumomediastinum (yellow arrows) and subcutaneous emphysema (yellow arrowheads). From: Iriarte CU et al. (42)



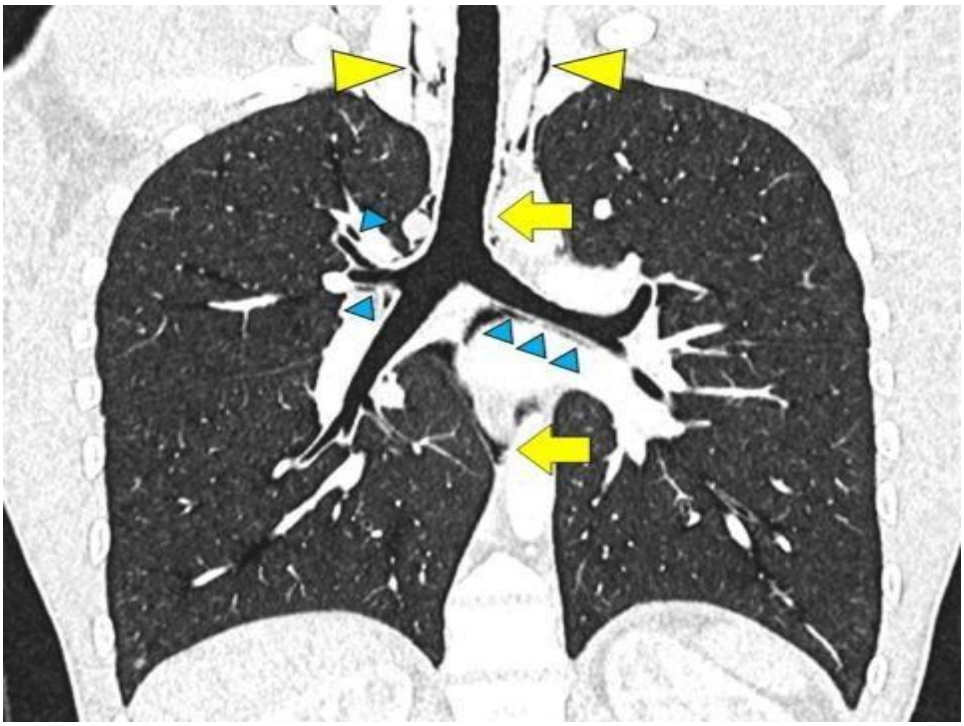
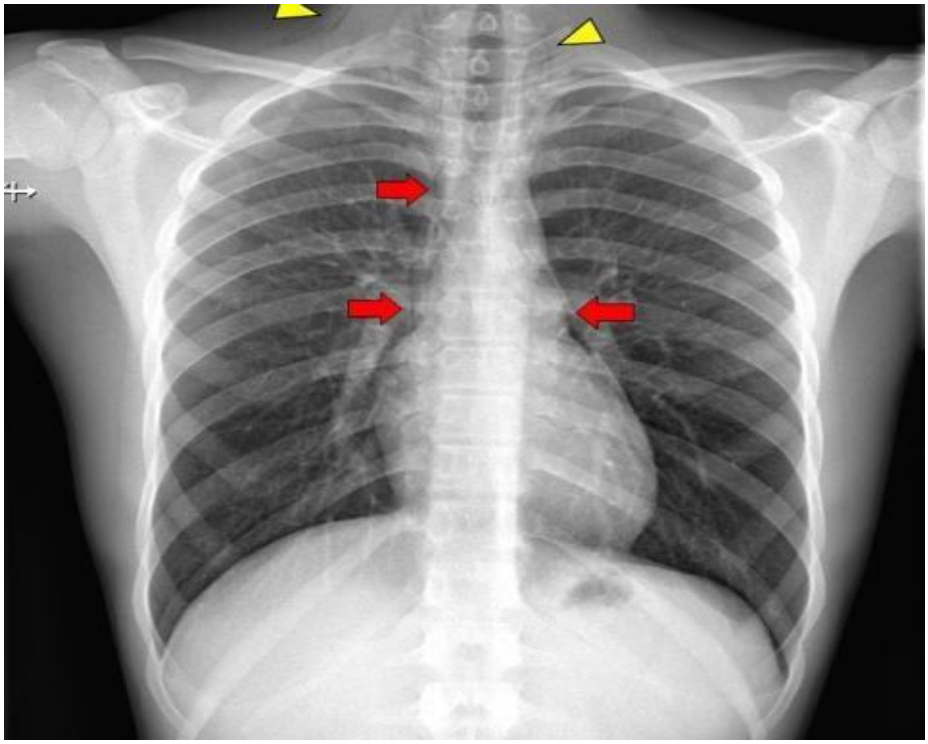


Fig. 23: **Chest X-rays** pa,

a): linear lucencies along pulmonary hila and paratracheal regions (red arrows) with subcutaneous emphysema (yellow arrowheads), from Iriarte, (42)

b) pneumomediastinum, massive subcutaneous and soft tissue emphysema and bilateral chest tubes for pneumothorax drainage in another patient

a



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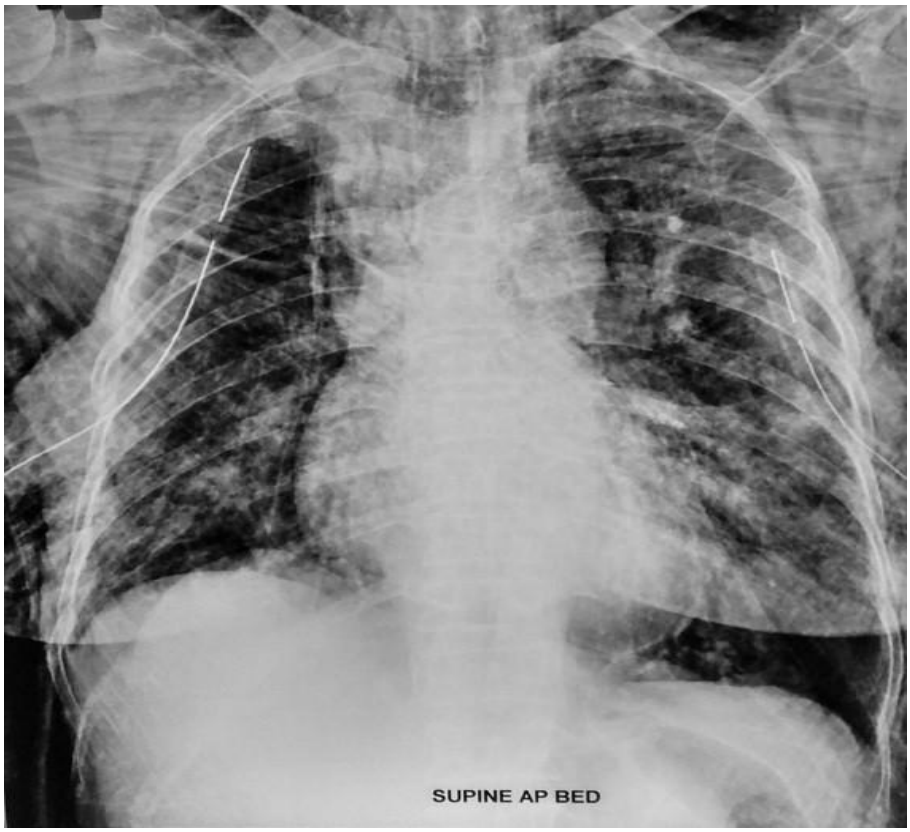
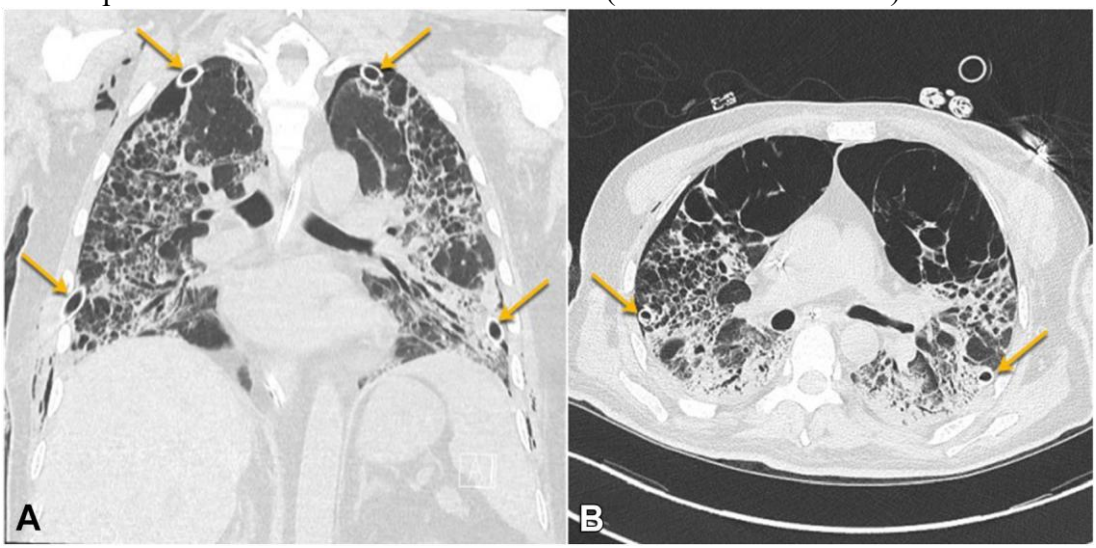


6.5.2. Development of Parenchymal Destruction and Cystic Pulmonary Lesions (Case 1)

Following inflammatory parenchymal lung destruction (Fig. 24) in severe COVID-19 pneumonia, together with sustained-pressure ventilation to obtain acceptable gas exchanges may lead to the buildup of multiple cystic lesions (16, 42, 43). In this setting, fibrotic parenchyma and the blebs are prone to rupture with consequent risk of pneumothorax.

Fig. 24: Cystic parenchymal destruction and bilateral tube thoracostomy drainage (arrows) in an 38-year-old patient with severe COVID-19 disease (from Geraci et al.: 43)



On the other hand, these cystic lesions can resolve completely in follow-up CT studies as shown in the following case **Case Nr. 1** (45, Fig. 25 + 26).

Fig. 25: Development of several subpleural cystic lesions and pneumothorax in the course of COVID-19 pneumonia (Case 1, from: Yagyu et al. (45) (A: axial, B coronal chest-CT)

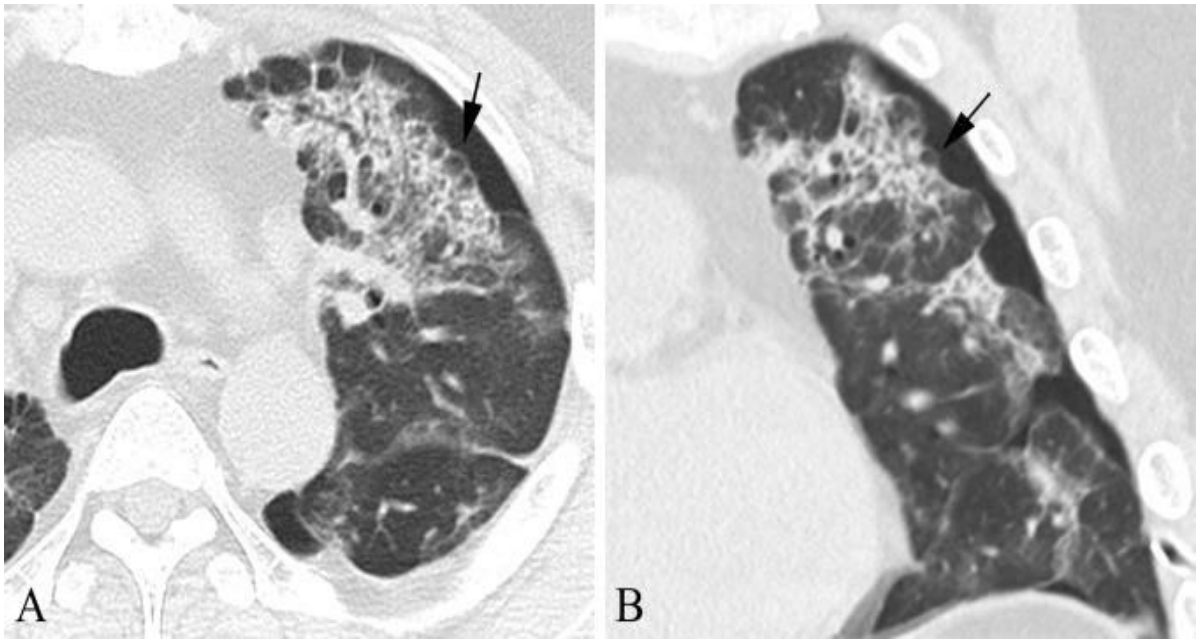
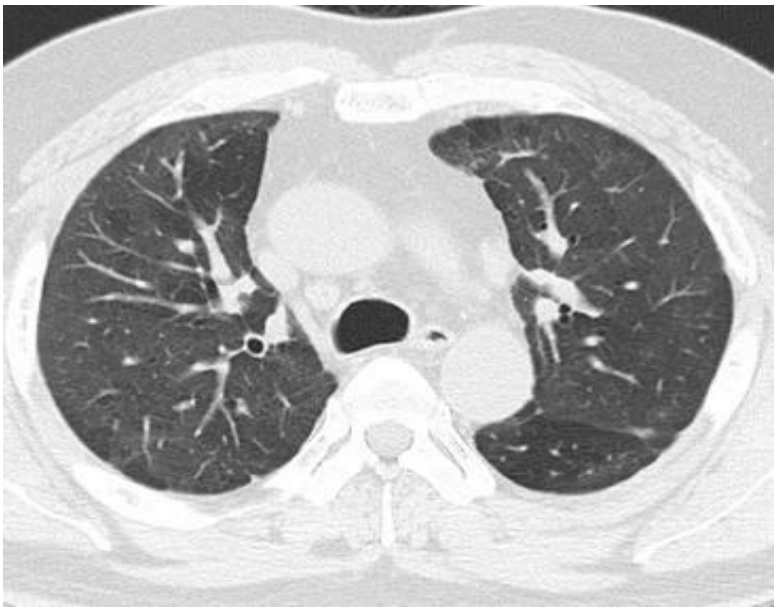


Fig. 26: The same patient, cystic lesions had resolved completely one month after discharge.



6.5.3. Pneumatoceles and Development of Pneumothorax (Case 2)

Pneumatoceles are cystic spaces that develop in the lung probably following cystic lesions in COVID-19 pneumonia and can lead to spontaneous pneumothorax.
Pneumatoceles are often asymptomatic and occur after insult to the lung parenchyma such as bacterial or viral pneumonia. Although they are predominantly infectious in cause, they may develop from other pathophysiological mechanisms including trauma, positive pressure ventilation, surgery, burns and diffuse interstitial pulmonary emphysema. This **Case 2** was presented by Utku Ekin et al. (46, Fig. 27 - 30).

Fig. 27. 43-year old woman with COVID-19 pneumonia, 7 days after onset of symptoms, now presenting with progressive shortness of breath, hypoxia and tachycardia, cough and fever. Initial radiograph of the chest demonstrated a **large bulla** of the upper lobe of the right lung. *Orange arrows* point to the inferior border of the bulla. Some lung tissue markings can be seen behind the air-filled space. From Utku, E. et al. (46).

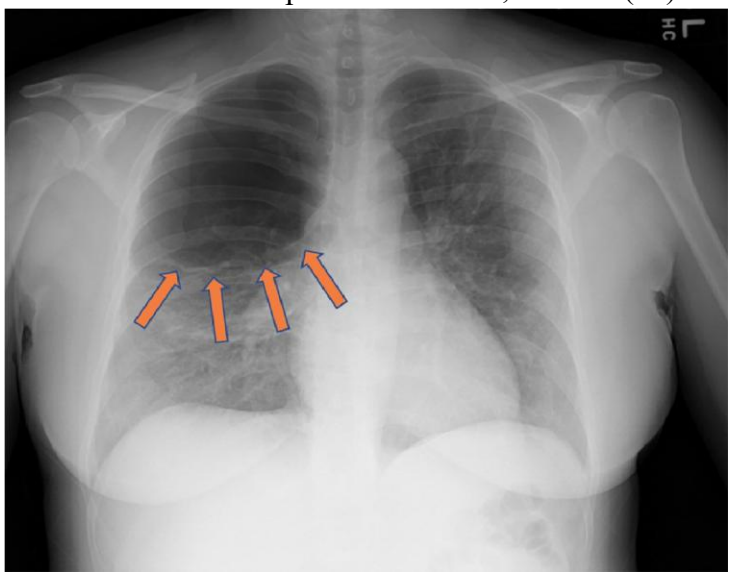
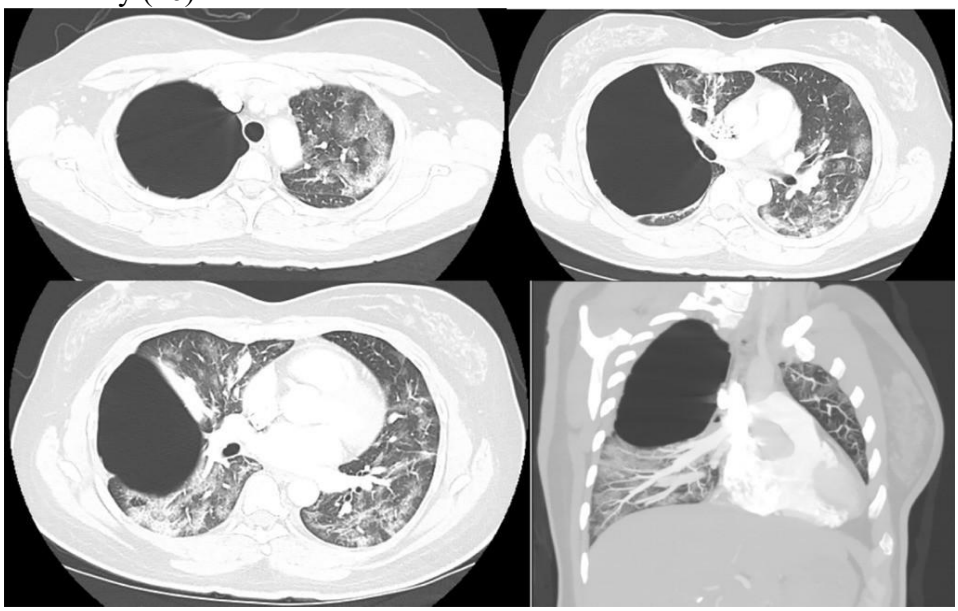


Fig. 28. A computed tomography of the thorax demonstrates a large right-sided P**neumatocele**. Ground-glass opacities are appreciated in the remaining lung parenchyma bilaterally (46).



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A few days later, the patient exhibited severe right-sided chest pain and shortness of breath. The Chest-X-ray showed a new right-sided pneumothorax (Fig. 29), the CT scan demonstrated a moderate-sized right pneumothorax and a persisting large right pneumatocele.

Fig. 29 . Chest radiograph demonstrates right-sided **pneumothorax**. *Orange arrows* point to the collapsed lung border.

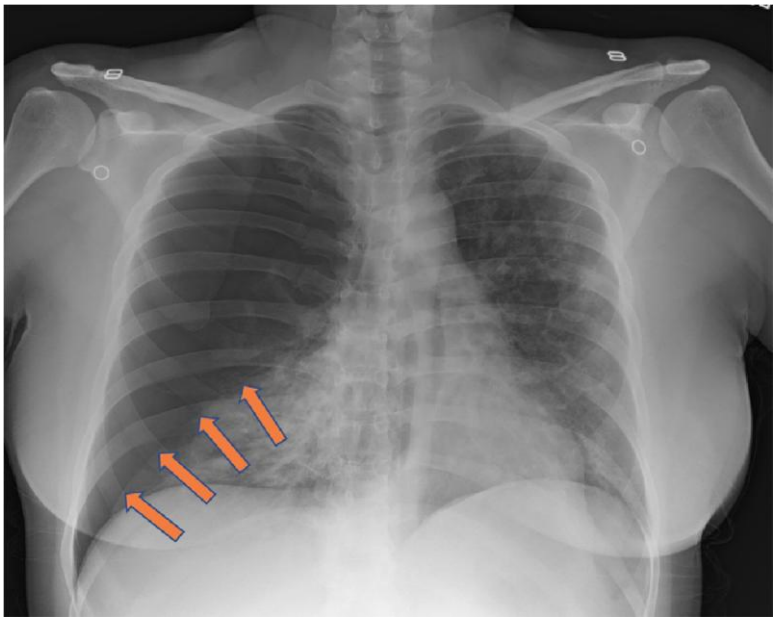
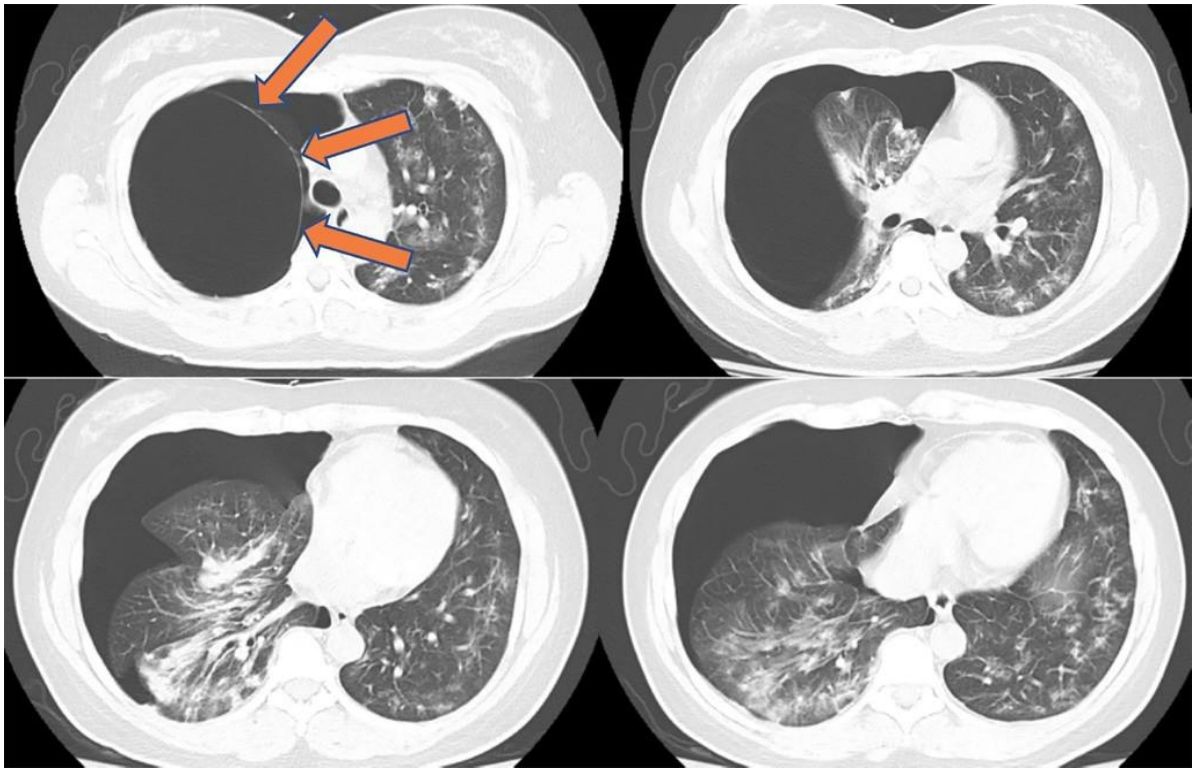


Fig. 30. Computed tomography of the thorax demonstrates large **pneumatocele** of the right lung as well as **pneumothorax** with collapsed portions of the right lung. *Orange arrows* point to the thin wall of the pneumatocele.



The cardiothoracic surgery team was consulted and the patient had right-sided thoracic drainage. However, the air leak persisted with no change in the size of the pneumothorax and it was decided to proceed with a video-assisted thoracic surgery (VATS), resecting the pneumatocele, right upperlobe wedge resection and lysis of pleural adhesions. Four days after surgery, the chest tubes were removed and shortly after the patient was discharged home in stable condition.

6.5.4. Development of Bronchopleural Fistula (Cases 3 and 4)

Placik et al (47, Fig. 31 - 33) present a case study of a 49-year old male who developed a tension pneumothorax 2 weeks after admission to hospital for COVID-19-pneumonia treated with antibiotics, antiviral therapy, high-dose glucocorticoids and interleukin antagonists.

A bronchopleural fistula is a communication with the pleural space and bronchial tree that results in high morbidity and mortality. It is most commonly recognized as a postoperative complication of pulmonary resection, however other commonly contributing factors include necrotizing pulmonary infection, persistent pneumothorax, chemotherapy and radiation therapy.

Pulmonary co-infections with staphylococcus aureus and fungal infections with aspergillus in immunocompromised patients may result especially from immunosuppressive therapy such as high-dose glucocorticoids and interleukin antagonists.

Fig. 31: Initial chest X-ray on presentation reveling typical **SARS-COV-2 pneumonia** without any evidence of right upper lobe lesions (From Placik et al., 47).

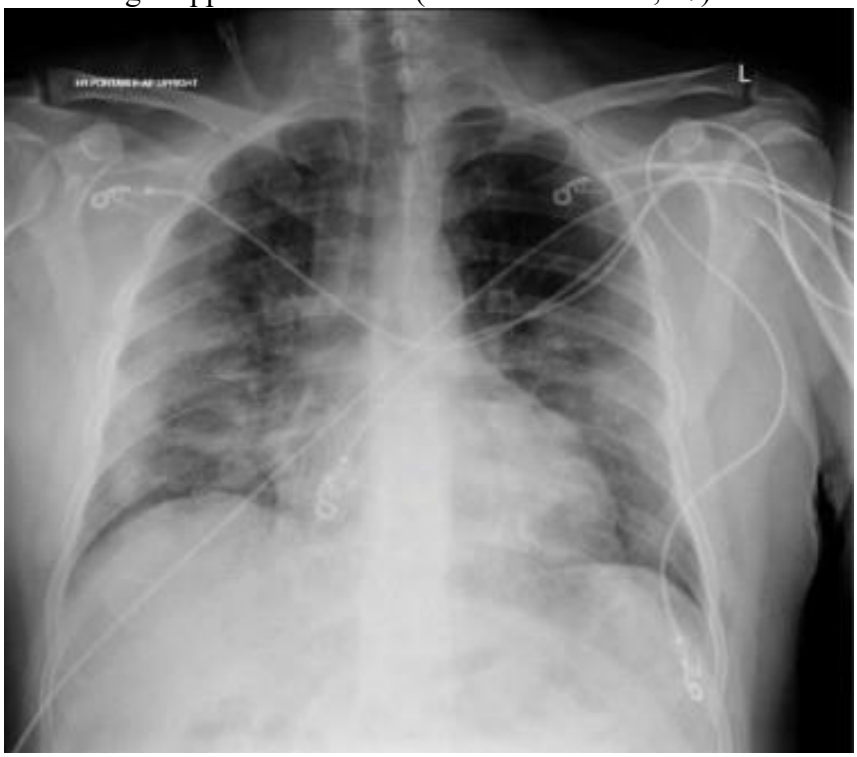
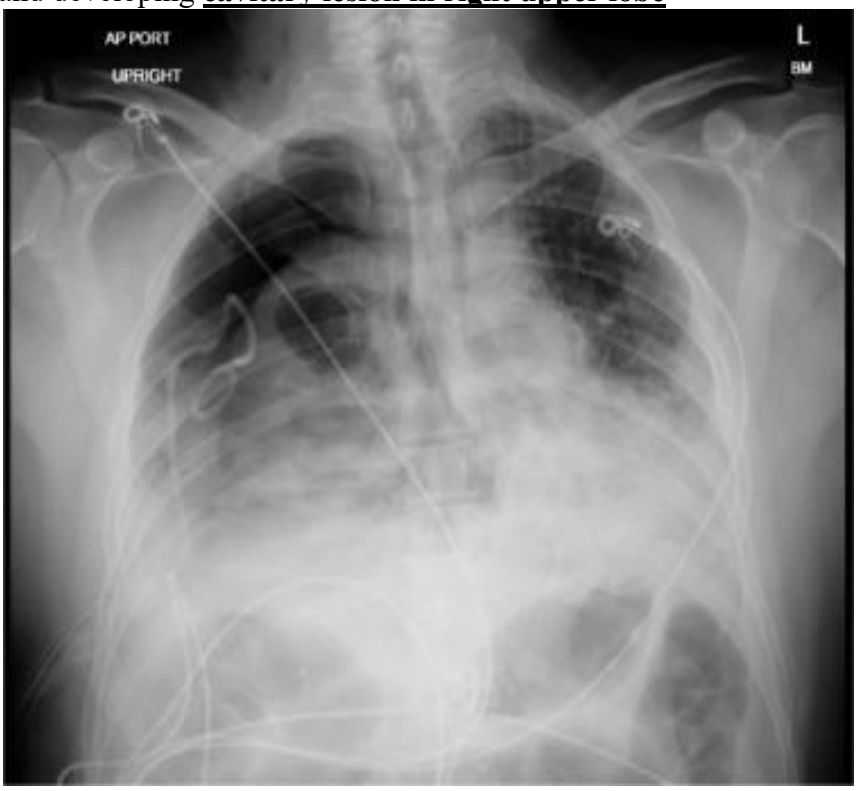
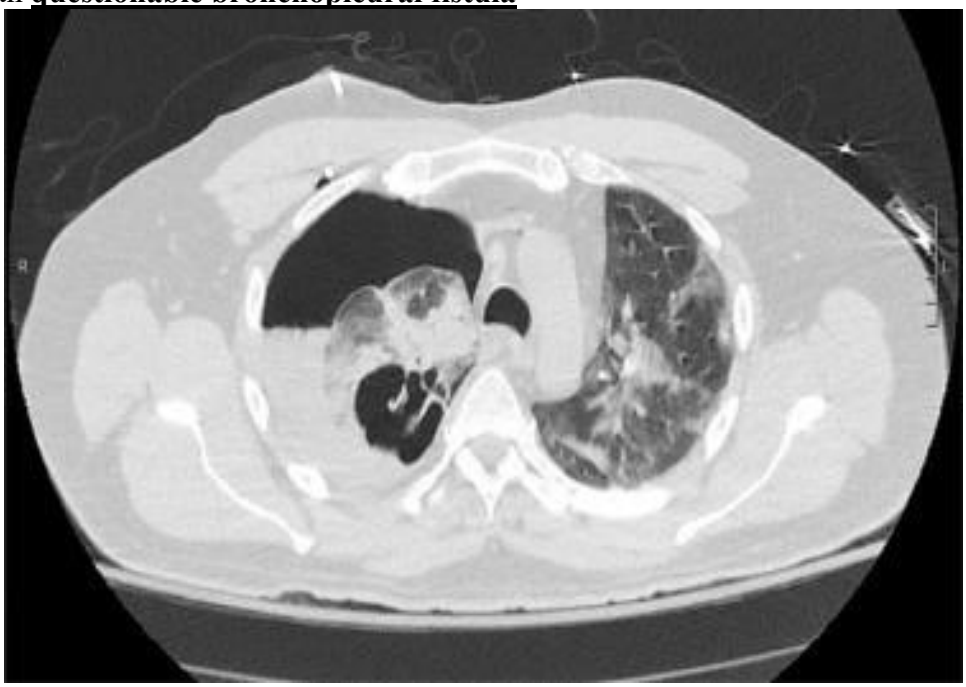


Fig. 32: 2 Weeks later, Chest X-ray showing bilateral pneumonia with a **persistent right pneumothorax** and developing **cavitary lesion in right upper lobe**



Follow-up chest CT showed a large air-filled bullous process / pneumatocele in the posterior right upper lobe, suspicious for bronchopulmonary fistula. He underwent thoracic surgery for persistent pneumothorax despite placement of chest tubes.

Fig. 33: Chest CT revealing a persistent **right pneumothorax** and an air-filled bullous process with **questionable bronchopleural fistula**



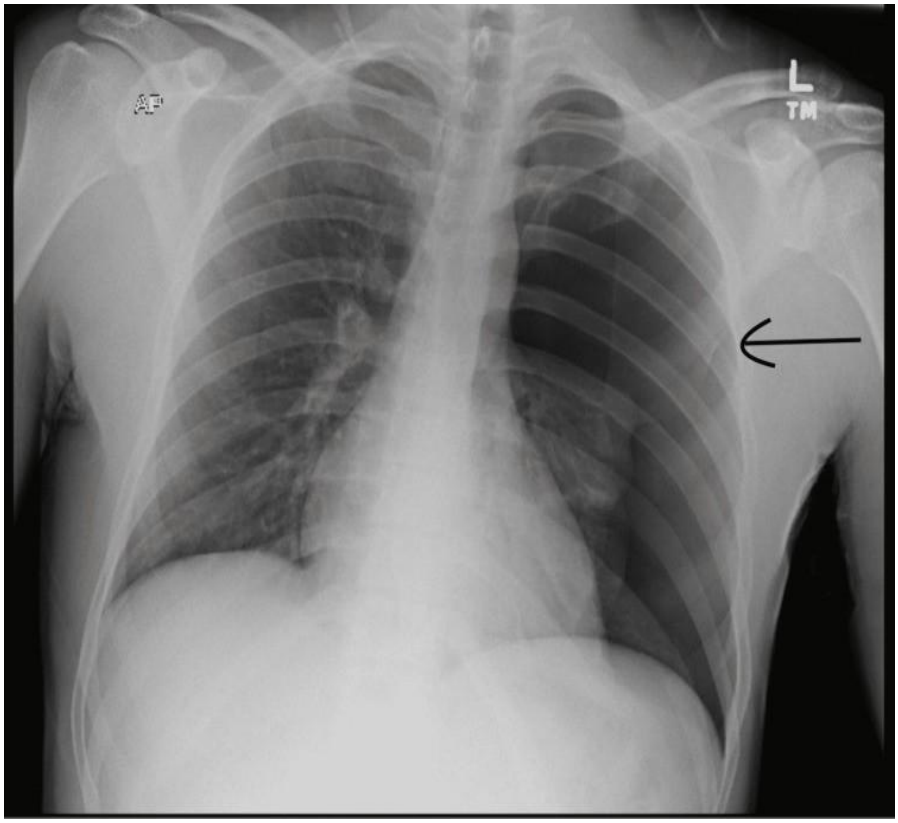
Thoracic surgery showed a large bronchopleural fistula of the right upper lobe with associated empyema. Pathological evaluation and microbiological analysis revealed a fungal infection with Rhizopus species. The hyphae are known to be angioinvasive, causing necrosis and thrombosis.

Smith et al. (48) describe the case **(Case 4)** of a young male who developed a pneumothorax complicating COVID-19 pneumonia and was found to have an empyema and bronchopleural fistula secondary to Staphylococcus aureus superinfection.
He had been diagnosed with COVID-19 by PCR 4 weeks prior and presented to ED complaining of left-sided chest pain without shortness of breath for the past two days.
Chest X-ray demonstrated a large left pneumothorax with complete collapse of the left lung (Fig.34). A chest tube was placed and put to suction.
Several days following chest tube placement, chest X-rays demonstrated resolution of the pneumothorax and complete expansion of the lung.
6 days later an X-ray showed recurrence of a large left pneumothorax despite the chest tube.

Video-assisted thoracoscopy on day 8 showed a left-sided empyema and bronchopleural fistula.
A left upper lobe wedge resection and mechanical pleurodesis were performed successfully.
After antibiotic therapy for the S. aureus superinfection, the patient was discharged home 14 days later.

Fig. 34: Large **left pneumothorax with complete left lung collapse** in a 26-year old man 4

weeks after diagnose of COVID-19. From Smith et al. (48).



7. COVID-19 and Pneumothorax

Two important causes in case of sudden respiratory compromise specifically related to COVID-19infected patients have been reported:

The first is pulmonary embolism (49), which occurs with a higher prevalence in COVID-19 patients.
The second is pneumothorax.

Both conditions need prompt diagnosis and intervention, being a critical emergency.

Pneumothorax is a rare complication of COVID-19-pneumonia that can occur in any stage of the disease, even as a late-sequel consequence a month after the diagnosis of COVID-19 as shown in Case 4 in 6.5.4 (48).

In the first months of the COVID-19 pandemic, mostly case reports (32, 34 - 38 and 43 - 48) have been published, meanwhile there is an increasing number of large retrospective studies and case series of pneumothorax and/or pneumomediastinum (3, 33, 49, 50).

Ershadi et al. (33) published a retrospective clinical study in 2023 and found 67 patients with pneumothorax out of 9800 hospitalized COVID-19 patients (0,68%), 18,6% of whom showed bilateral pneumothoraces.

Zantah et al (50) published a review of 902 COVID-19-positive patients showing a pneumothorax prevalence of 0,66%.
Martinelli et al. (51) had a case series of 60 COVID-19 patients with pneumothorax and 11 with pneumomediastinum out of 6574 COVID-19 hospital admissions from 16 centres in the UK, giving an incidence of 0,91%.

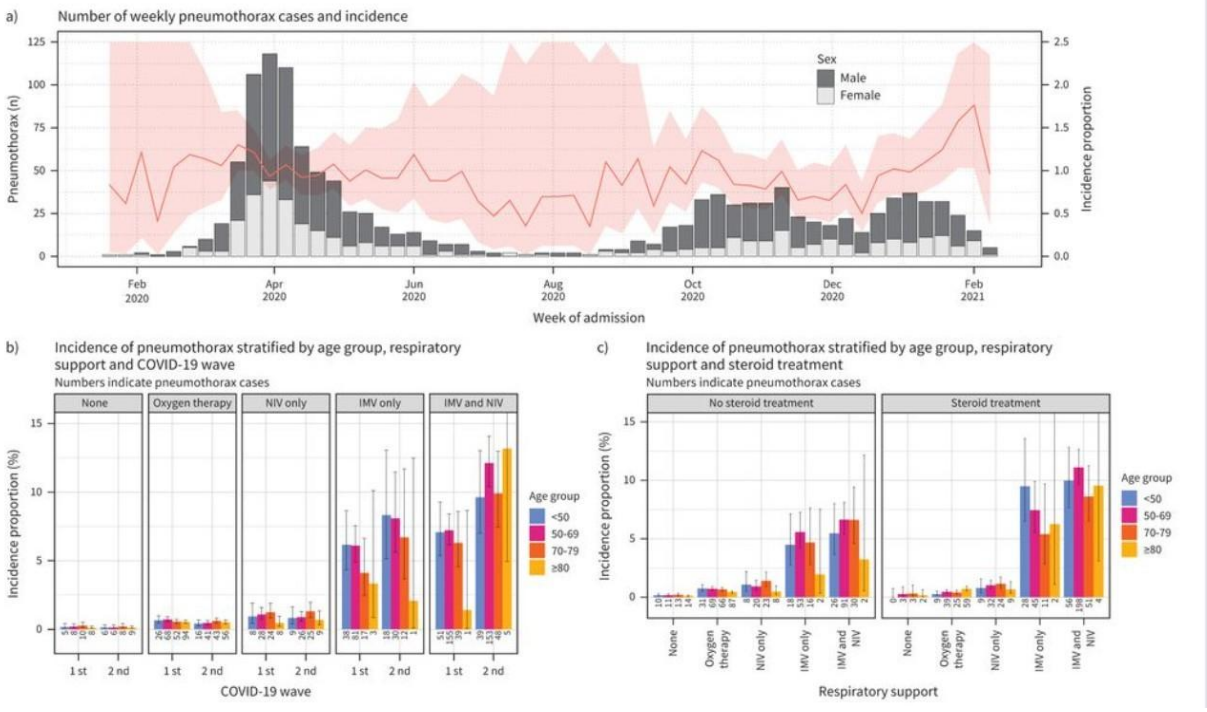
Geraci et al (43) had a high incidence of 7,4 % (118 patients with pneumothorax out of 1595 admitted for COVID-19) in a retrospective review of a single-institution (Division of Thoracic Surgery, New York University Langone Health) in the first months (March – April 2020) of the pandemic, possibly a consequence of the high proportion of mechanical ventilated patients (80,5%) at the time of pneumothorax onset.
In comparison to that, Ershadi`s study (33), 39% of patients had previous oxygen masks, 14,3% non-invasive ventilation (NIV) and only 21,4% were intubated.

COVID-19 patients requiring noninvasive or invasive ventilatory support appeared at elevated risk for barotrauma (pneumothorax and / or pneumomediastinum) and this was found to be an independent risk for death.

The treatment with dexomethasone in COVID-19 patients receiving respiratory support reduces 28-day mortality (54, Preliminary Report), but may rise the incidence of pneumothorax by inducing lung frailty and delay of the healing process and thus increases the risk of pneumothorax (43).

Older patients aged over 70 years had a significant lower 28-day survival than youger individuals.

Fig. 35: COVID-19 pneumothorax in ISARIC4C dataset (from Marciniak et al: 55).
a) Histogram of incidence of pneumothoraces over time (absolute numbers, light grey females, dark grey males), line graph of pneumothorax incidence.
b) Incidence of pneumothorax by age, ventilatory support and pandemic wave.
c) Incidence of pneumothorax by age, ventilatory support and steroid therapy: NIV: noninvasive respiratory support, IMV: invasive respiratory support.



Patients with neutrophilia or otherwise immunocompromised, extensive lung damage and protracted clinical course with bacterial or fungal superinfection were more likely to experience pneumothorax.

Chest drain was inserted in 80,6%, in 6% chest drain and surgery, conservatively 13,4%.

Overall mortality was high: 52,5% (52), respectively 66,6% (50) and 58% (43).
The average survival time for deceased patients was 10 days. In all cases, mortality was not directly related to the pneumothorax.

Predictors of survival (35):
Severity and duration of COVID-19-induced pneumonia and lung damage / ARDS, bacterial or fungal superinfection and barotrauma from mechanical ventilation raise the probability of PTX.
The build-up of bullae / cystic lung lesions and pleural effusion are prognostic factors for a poor outcome.
The lowest survival rate showed patients with bullae and pleural effusion in chest CT.
There was no significant correlation to demograhic factors (age, sex, BMI and smoking).

8. Treatment of Pneumothorax in COVID-19 patients

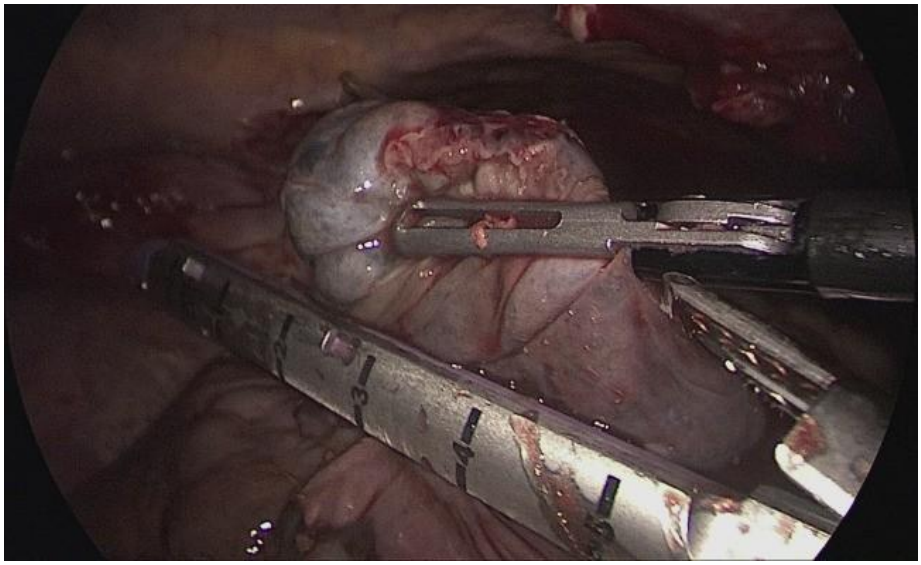
ARDS is the most common indication for transferring patients with COVID-19 to the ICU and the major cause of death in these patients.
In comparison to other forms of ARDS and inflammatory lung disease there is a higher risk of barotrauma in patients with COVID-19, even without positive pressure ventilation / IMV use (7).

PTX treatment in COVID-19 patients might be more challenging than usual.
Prompt recognition of early signs and symptoms is necessary to minimize morbidity and mortality
It is still unrecognized if there are inherent unique mechanisms to COVID-19 which predisposes patients to exaggerated inflammatory response resulting in alveolar injury that affects respiratory mechanics resulting in barotrauma at a higher rate than other viral pneumonia.

Generally air leaks were described as larger and a high rate (21%) of tension physiology was described by Geraci (43), possibly due to the high levels of positive pressure being used to oxygenate COVID-19 patients.
So small-bore chest tubes were described as ineffective as they less likely led to full lung expansion and often became obstructed.
In COVID-19-related PTX and heavy lung damage / ARDS, large-sized chest tubes and permanent aspiration is recommended.

In case of persistent air leak, minimal invasive thoracoscopy / VATS with bleb/bulla - resection may be indicated (44, Fig. 25).

Fig. 25: Thoracic Surgery: Blebs are grasped and resected (From Aiolfi et al., 44)



9. Conclusions

Pneumothorax is a rare, but serious complication in COVID-19 pneumonia as survival rate is signifinantly lower than without.

The proposed mechanisms of pneumothorax-buildup in patients with COVID-19 disease is thought to be infection-/ inflammation-related alveolar damage.
Alveolar wall rupture brought on by increased airway pressure form intense coughing or barotrauma from mechanical ventilation especially in case of inflammation-induced lung damage and the high airway pressures used in the treatment of ARDS may be the primary cause leading to formation of subpleural air cysts and pulmonary bullae / pneumatocele.
However, pneumothorax can occur in patients over 2 weeks post extubation or in patients not intubated at all.
In this case, fibromyxoid exudates could create a valve effect in the bronchi, bronchial distortion and narrowing and may precipitate bulla rupture and pneumothorax formation.

Nevertheless, intubated patients have a higher risk of developing these complications, especially in case of cortocosteroid medication that might promote lung frailty.

In case of bacterial or fungal superinfection especially in immunocompromised patients, the formation of lung abscess, pleural empyema and bronchopleural fistula may lead to pneumothorax and persistent air leakage.

Chest drainage represents the first-line treatment for pneumothorax in COVID-19 pneumonia even in small penumothoraces as lung capacity may be already highly reduced.
However, in cases of persistent pneumothorax, bronchopleural fistula, lung abscess and / or pleural empyema, thoracic surgery, wedge- / bleb-resection and pleurectomy may be required to fix air leakage and persistent pneumothorax.

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